Description

BIOINFORMATICALLY DETECTABLE GROUP OF NOVEL HIV REGULATORY GENES AND USES THEREOF

BACKGROUND OF INVENTION

FIELD OF THE INVENTION

[0001] The present invention relates to a group of bioinformatically detectable novel viral RNA regulatory genes, here identified as "viral genomic address messenger"or "VGAM"genes.

DESCRIPTION OF PRIOR ART

[0002] Small RNAs are known to perform diverse cellular functions, including post-transcriptional gene expression regulation. The first two such RNA genes, Lin-4 and Let-7, were identified by genetic analysis of Caenorhabditis Elegans (Elegans) developmental timing, and were termed short temporal RNA (stRNA) (Wightman, B., Ha, I., Ruvkun, G., Cell 75, 855 (1993); Erdmann, V.A.. et al., Nucleic

Acids Res. 29, 189 (2001); Lee, R. C., Feinbaum, R. L., Ambros, V., Cell 75, 843 (1993); Reinhart, B. et al., Nature 403, 901 (2000)).

[0003] Lin-4 and Let-7 each transcribe a ~22 nucleotide (nt) RNA, which acts a post transcriptional repressor of target mRNAs, by binding to elements in the 3"-untranslated region (UTR) of these target mRNAs, which are complimentary to the 22 nt sequence of Lin-4 and Let-7 respectively. While Lin-4 and Let-7 are expressed at different developmental stage, first larval stage and fourth larval stage respectively, both specify the temporal progression of cell fates, by triggering post-transcriptional control over other genes (Wightman, B., Ha, I., Ruvkun, G., Cell 75, 855 (1993); Slack et al., Mol.Cell 5 ,659 (2000)). Let-7 as well as its temporal regulation have been demonstrated to be conserved in all major groups of bilaterally symmetrical animals, from nematodes, through flies to humans (Pasquinelli, A., et al. Nature 408 ,86 (2000)).

[0004] The initial transcription product of Lin-4 and Let-7 is a ~60-80nt RNA, the nucleotide sequence of the first half of which is partially complimentary to that of its second half, therefore allowing this RNA to fold onto itself, forming a "hairpin structure". The final gene product is a ~22nt RNA,

which is "diced" from the above mentioned "hairpin struc-
ture", by an enzyme called Dicer, which also apparently
also mediates the complimentary binding of this ~22nt
segment to a binding site in the 3" UTR of its target gene.

[0005] Recent studies have uncovered 93 new genes in this class,
now referred to as micro RNA or miRNA genes, in
genomes of Elegans, Drosophilea, and Human
(Lagos-Quintana, M., Rauhut, R., Lendeckel, W., Tuschl,
T., Science 294 ,853 (2001); Lau, N.C., Lim, L.P., Wein-
stein, E.G., Bartel, D.P., Science 294 ,858 (2001); Lee, R.C.,
Ambros, V., Science 294 ,862 (2001). Like the well studied
Lin-4 and Let-7, all newly found MIR genes produce a
~60-80nt RNA having a nucleotide sequence capable of
forming a "hairpin structure". Expressions of the precursor
~60-80nt RNA and of the resulting diced ~22nt RNA of
most of these newly discovered MIR genes have been de-
tected.

[0006] Based on the striking homology of the newly discovered
MIR genes to their well-studied predecessors Lin-4 and
Let-7, the new MIR genes are believed to have a similar
basic function as that of Lin-4 and Let-7: modulation of
target genes by complimentary binding to the UTR of
these target genes, with special emphasis on modulation

of developmental control processes. This is despite the fact that the above mentioned recent studies did not find target genes to which the newly discovered MIR genes complementarily bind. While existing evidence suggests that the number of regulatory RNA genes "may turn out to be very large, numbering in the hundreds or even thousands in each genome", detecting such genes is challenging (Ruvkun G., "Perspective: Glimpses of a tiny RNA world", Science 294 ,779 (2001)).

[0007] The ability to detect novel RNA genes is limited by the methodologies used to detect such genes. All RNA genes identified so far either present a visibly discernable whole body phenotype, as do Lin-4 and Let-7 (Wightman et. al., Cell 75, 855 (1993); Reinhart et al., Nature 403, 901 (2000)), or produce significant enough quantities of RNA so as to be detected by the standard biochemical genomic techniques, as do the 93 recently detected miRNA genes. Since a limited number clones were sequenced by the researchers discovering these genes, 300 by Bartel and 100 by Tuschl (Bartel et. al., Science 294 ,858 (2001); Tuschl et. al., Science 294 ,853 (2001)), the RNA genes found can not be much rarer than 1% of all RNA genes. The recently detected miRNA genes therefore represent the more

prevalent among the miRNA gene family.

[0008] Current methodology has therefore been unable to detect RNA genes which either do not present a visually discernable whole body phenotype, or are rare (e.g. rarer than 0.1% of all RNA genes), and therefore do not produce significant enough quantities of RNA so as to be detected by standard biochemical technique.To date, miRNA have not been detected in viruses.

SUMMARY OF INVENTION

[0009] The present invention relates to a novel group of bioinformatically detectable, viral regulatory RNA genes, which repress expression of host target host genes, by means of complementary hybridization to binding sites in untranslated regions of these host target host genes. It is believed that this novel group of viral genes represent a pervasive viral mechanism of attacking hosts, and that therefore knowledge of this novel group of viral genes may be useful in preventing and treating viral diseases.

[0010] In various preferred embodiments, the present invention seeks to provide improved method and system for detection and prevention of viral disease, which is mediated by this group of novel viral genes.

[0011] Accordingly, the invention provides several substantially

pure nucleic acids (e.g., genomic nucleic acid, cDNA or synthetic nucleic acid) each encoding a novel viral gene of the VGAM group of gene, vectors comprising the nucleic acids , probes comprising the nucleic acids , a method and system for selectively modulating translation of known "target" genes utilizing the vectors, and a method and system for detecting expression of known "target" genes utilizing the probe.

[0012] By "substantially pure nucleic acid" is meant nucleic acid that is free of the genes which, in the naturally-occurring genome of the organism from which the nucleic acid of the invention is derived, flank the genes discovered and isolated by the present invention. The term therefore includes, for example, a recombinant nucleic acid which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic nucleic acid of a prokaryote or eukaryote at a site other than its natural site; or which exists as a separate molecule (e.g., a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant nucleic acid which is part of a hybrid gene encoding additional polypeptide sequence.

[0013] "Inhibiting translation" is defined as the ability to prevent synthesis of a specific protein encoded by a respective gene, by means of inhibiting the translation of the mRNA of this gene. "Translation inhibiter site" is defined as the minimal nucleic acid sequence sufficient to inhibit translation.

[0014] There is thus provided in accordance with a preferred embodiment of the present invention a bioinformatically detectable novel viral gene encoding substantially pure nucleic acid wherein: RNA encoded by the bioinformatically detectable novel viral gene is about 18 to about 24 nucleotides in length, and originates from an RNA precursor, which RNA precursor is about 50 to about 120 nucleotides in length, a nucleotide sequence of a first half of the RNA precursor is a partial inversed-reversed sequence of a nucleotide sequence of a second half thereof, a nucleotide sequence of the RNA encoded by the novel viral gene is a partial inversed-reversed sequence of a nucleotide sequence of a binding site associated with at least one host target gene, and a function of the novel viral gene is bioinformatically deducible.

[0015] There is further provided in accordance with another preferred embodiment of the present invention a method for

anti-viral treatment comprising neutralizing said RNA.

[0016] Further in accordance with a preferred embodiment of the present invention the neutralizing comprises: synthesizing a complementary nucleic acid molecule, a nucleic sequence of which complementary nucleic acid molecule is a partial inversed-reversed sequence of said RNA, and transfecting host cells with the complementary nucleic acid molecule, thereby complementarily binding said RNA.

[0017] Further in accordance with a preferred embodiment of the present invention the neutralizing comprises immunologically neutralizing.

[0018] There is still further provided in accordance with another preferred embodiment of the present invention a bioinformatically detectable novel viral gene encoding substantially pure nucleic acid wherein: RNA encoded by the bioinformatically detectable novel viral gene includes a plurality of RNA sections, each of the RNA sections being about 50 to about 120 nucleotides in length, and including an RNA segment, which RNA segment is about 18 to about 24 nucleotides in length, a nucleotide sequence of a first half of each of the RNA sections encoded by the novel viral gene is a partial inversed-reversed sequence of nucleotide sequence of a second half thereof, a nucleotide

sequence of each of the RNA segments encoded by the novel viral gene is a partial inversed-reversed sequence of the nucleotide sequence of a binding site associated with at least one target host gene, and a function of the novel viral gene is bioinformatically deducible from the following data elements: the nucleotide sequence of the RNA encoded by the novel viral gene, a nucleotide sequence of the at least one target host gene, and function of the at least one target host gene.

[0019] Further in accordance with a preferred embodiment of the present invention the function of the novel viral gene is bioinformatically deducible from the following data elements: the nucleotide sequence of the RNA encoded by the bioinformatically detectable novel viral gene, a nucleotide sequence of the at least one target host gene, and a function of the at least one target host gene.

[0020] Still further in accordance with a preferred embodiment of the present invention the RNA encoded by the novel viral gene complementarily binds the binding site associated with the at least one target host gene, thereby modulating expression of the at least one target host gene.

[0021] Additionally in accordance with a preferred embodiment of the present invention the binding site associated with

at least one target host gene is located in an untranslated region of RNA encoded by the at least one target host gene.

[0022] Moreover in accordance with a preferred embodiment of the present invention the function of the novel viral gene is selective inhibition of translation of the at least one target host gene, which selective inhibition includes complementary hybridization of the RNA encoded by the novel viral gene to the binding site.

[0023] Further in accordance with a preferred embodiment of the present invention the invention includes a vector including the DNA.

[0024] Still further in accordance with a preferred embodiment of the present invention the invention includes a method of selectively inhibiting translation of at least one gene, including introducing the vector.

[0025] Moreover in accordance with a preferred embodiment of the present invention the introducing includes utilizing RNAi pathway.

[0026] Additionally in accordance with a preferred embodiment of the present invention the invention includes a gene expression inhibition system including: the vector, and a vector inserter, functional to insert the vector into a cell,

thereby selectively inhibiting translation of at least one gene.

[0027] Further in accordance with a preferred embodiment of the present invention the invention includes a probe including the DNA.

[0028] Still further in accordance with a preferred embodiment of the present invention the invention includes a method of selectively detecting expression of at least one gene, including using the probe.

[0029] Additionally in accordance with a preferred embodiment of the present invention the invention includes a gene expression detection system including: the probe, and a gene expression detector functional to selectively detect expression of at least one gene.

[0030] Further in accordance with a preferred embodiment of the present invention the invention includes an anti-viral substance capable of neutralizing the RNA.

[0031] Still further in accordance with a preferred embodiment of the present invention the neutralizing includes complementarily binding the RNA.

[0032] Additionally in accordance with a preferred embodiment of the present invention the neutralizing includes immunologically neutralizing.

[0033] Moreover in accordance with a preferred embodiment of the present invention the invention includes a method for anti-viral treatment including neutralizing the RNA.

[0034] Further in accordance with a preferred embodiment of the present invention the neutralizing includes: synthesizing a complementary nucleic acid molecule, a nucleic sequence of which complementary nucleic acid molecule is a partial inversed-reversed sequence of the RNA, and transfecting host cells with the complementary nucleic acid molecule, thereby complementarily binding the RNA.

[0035] Still further in accordance with a preferred embodiment of the present invention the neutralizing includes immuno-logically neutralizing.

BRIEF DESCRIPTION OF DRAWINGS

[0036] Fig. 1 is a simplified diagram illustrating a mode by which viral genes of a novel group of viral genes of the present invention, modulate expression of known host target genes;

[0037] Fig. 2 is a simplified block diagram illustrating a bioinfor-matic gene detection system capable of detecting genes of the novel group of genes of the present invention, which system is constructed and operative in accordance with a preferred embodiment of the present invention;

[0038]   Fig. 3 is a simplified flowchart illustrating operation of a
          mechanism for training of a computer system to recog-
          nize the novel genes of the present invention, which
          mechanism is constructed and operative in accordance
          with a preferred embodiment of the present invention;

[0039]   Fig. 4A is a simplified block diagram of a non-coding ge-
          nomic sequence detector constructed and operative in ac-
          cordance with a preferred embodiment of the present in-
          vention;

[0040]   Fig. 4B is a simplified flowchart illustrating operation of a
          non-coding genomic sequence detector constructed and
          operative in accordance with a preferred embodiment of
          the present invention;

[0041]   Fig. 5A is a simplified block diagram of a hairpin detector
          constructed and operative in accordance with a preferred
          embodiment of the present invention;

[0042]   Fig. 5B is a simplified flowchart illustrating operation of a
          hairpin detector constructed and operative in accordance
          with a preferred embodiment of the present invention;

[0043]   Fig. 6A is a simplified block diagram of a dicer-cut loca-
          tion detector constructed and operative in accordance
          with a preferred embodiment of the present invention;

[0044]   Fig. 6B is a simplified flowchart illustrating training of a

dicer-cut location detector constructed and operative in accordance with a preferred embodiment of the present invention;

[0045] Fig. 7A is a simplified block diagram of a target-gene binding-site detector constructed and operative in accordance with a preferred embodiment of the present invention;

[0046] Fig. 7B is a simplified flowchart illustrating operation of a target-gene binding-site detector constructed and operative in accordance with a preferred embodiment of the present invention;

[0047] Fig. 8 is a simplified flowchart illustrating operation of a function & utility analyzer constructed and operative in accordance with a preferred embodiment of the present invention;

[0048] Fig. 9 is a simplified diagram describing a novel bioinformatically detected group of regulatory genes, referred to here as Genomic Record (GR) genes, each of which encodes an "operon-like" cluster of novel miRNA-like genes, which in turn modulates expression of a plurality of target genes;

[0049] Fig. 10 is a block diagram illustrating different utilities of genes of a novel group of genes, and operons of a novel

group of operons, both of the present invention;

[0050] Figs. 11A and 11B are simplified diagrams, which when taken together illustrate a mode of gene therapy applicable to genes of the novel group of genes of the present invention;

[0051] Fig. 12A is an annotated sequence of EST72223 comprising novel gene GAM24 detected by the gene detection system of the present invention;

[0052] Figs. 12B and 12C are pictures of laboratory results, which when taken together demonstrate laboratory confirmation of expression of the bioinformatically detected novel gene GAM24 of Fig. 12A;

[0053] Fig. 12D provides pictures of laboratory results, which when taken together demonstrate further laboratory confirmation of expression of the bioinformatically detected novel gene GAM24 of Fig. 12A;

[0054] Fig. 13A is an annotated sequence of an EST7929020 comprising novel genes GAM23 and GAM25 detected by the gene detection system of the present invention;

[0055] Fig. 13B is a picture of laboratory results, which confirm expression of bioinformatically detected novel genes GAM23 and GAM25 of Fig. 13A;

[0056] Fig. 13C is a picture of laboratory results, which confirm

endogenous expression of bioinformatically detected novel gene GAM25 of Fig. 15A;

[0057] Fig. 14A is an annotated sequence of an EST1388749 comprising novel gene GAM26 detected by the gene detection system of the present invention;

[0058] Figs. 14B is a picture of laboratory results, which confirm expression of the bioinformatically detected novel gene GAM26 of Fig. 14A;

[0059] Figs. 15A through 29D are schematic diagrams illustrating sequences, functions and utilities of 15 specific viral genes of the novel group of viral regulatory genes of the present invention, detected using the bioinformatic gene detection system described hereinabove with reference to Figs. 1 through 8; and

[0060] Figs. 30 through 31 are schematic diagrams illustrating sequences, functions and utilities of 2 specific viral genes of a group of novel regulatory "operon-like" viral genes of the present invention, detected using the bioinformatic gene detection system described hereinabove with reference to Figs. 9 through 14.

BRIEF DESCRIPTION OF SEQUENCES

[0061] A Sequence Listing of genomic sequences of the present invention designated SEQ ID:1 through SEQ ID:406 is at-

tached to this application, enclosed in computer readable form on CD-ROM. The genomic listing comprises the following nucleotide sequences:Genomic sequences designated SEQ ID:1 through SEQ ID:15 are nucleotide sequences of 15 gene precursors of respective novel genes of the present invention;Genomic sequences designated SEQ ID:16 through SEQ ID:30 are nucleotide sequences of 15 genes of the present invention; andGenomic sequences designated SEQ ID:31 through SEQ ID:406 are nucleotide sequences of 376 gene precursors of respective novel genes of the present invention.

DETAILED DESCRIPTION

[0062]   Reference is now made to Fig. 1 which is a simplified diagram illustrating a mode by which genes of a novel group of genes of the present invention, modulate expression of known host target.

[0063]   The novel genes of the present invention are micro RNA (miRNA)-like, regulatory RNA genes, modulating expression of known host target. This mode of modulation is common to other known miRNA genes, as described hereinabove with reference to the background of the invention section.

[0064]   VGAM GENE and TARGET GENE are two human genes con-

tained in the DNA of the human genome.

[0065] VGAM GENE encodes a VGAM PRECURSOR RNA. However, similar to other miRNA genes, and unlike most ordinary genes, its RNA, VGAM PRECURSOR RNA, does not encode a protein.

[0066] VGAM PRECURSOR RNA folds onto itself, forming VGAM FOLDED PRECURSOR RNA. As Fig.8 illustrates, VGAM FOLDED PRECURSOR RNA forms a "hairpin structure", folding onto itself. As is well known in the art, this "hairpin structure", is typical genes of the miRNA genes, and is due to the fact that nucleotide sequence of the first half of the RNA of a gene in this group is an accurate or partial inversed-reversed sequence of the nucleotide sequence of its second half. By "inversed-reversed"is meant a sequence which is reversed and wherein each nucleotide is replaced by a complimentary nucleotide, as is well known in the art (e.g. ATGGC is the inversed-reversed sequence of GCCAT).

[0067] An enzyme complex, designated DICER COMPLEX, "dices" the VGAM FOLDED PRECURSOR RNA into a single stranded RNA segment, about 22 nucleotides long, designated VGAM RNA. As is known in the art, "dicing" of the hairpin structured RNA precursor into shorter RNA segments

about 22 nucleotides long by a Dicer type enzyme is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins.

[0068] TARGET GENE encodes a corresponding messenger RNA, designated TARGET RNA. This TARGET RNA comprises 3 regions: a 5" untranslated region, a protein coding region and a 3" untranslated region, designated 5"UTR, PROTEIN CODING and 3"UTR respectively.

[0069] VGAM RNA binds complementarily a BINDING SITE, located on the 3"UTR segment of TARGET RNA. This complementarily binding is due to the fact that the nucleotide sequence of VGAM RNA is an accurate or partial inversed-reversed sequence of the nucleotide sequence of BINDING SITE.

[0070] The complimentary binding of VGAM RNA to BINDING SITE inhibits translation of TARGET RNA into TARGET PROTEIN. TARGET PROTEIN is therefore outlined by a broken line.

[0071] It is appreciated by one skilled in the art that the mode of transcriptional inhibition illustrated by Fig. 1 with specific reference to VGAM genes of the present invention, is in fact common to all other miRNA genes. A specific complimentary binding site has been demonstrated only for Lin-4 and Let-7. All the other 93 newly discovered miRNA

genes are also believed by those skilled in the art to modulate expression of other genes by complimentary binding, although specific complimentary binding sites for these genes have not yet been found (Ruvkun G., "Perspective: Glimpses of a tiny RNA world", Science 294 ,779 (2001)). The present invention discloses a novel group of genes, the VGAM genes, belonging to the miRNA genes group, and for which a specific an complimentary binding has been determined.

[0072] Reference is now made to Fig. 2 which is a simplified block diagram illustrating a bioinformatic gene detection system capable of detecting genes of the novel group of genes of the present invention, which system is constructed and operative in accordance with a preferred embodiment of the present invention.

[0073] A centerpiece of the present invention is a bioinformatic gene detection engine 100, which is a preferred implementation of a mechanism capable of bioinformatically detecting genes of the novel group of genes of the present invention.

[0074] The function of the bioinformatic gene detection engine 100 is as follows: it receives three types of input, expressed RNA data 102, sequenced DNA data 104, and

protein function data 106, performs a complex process of analysis of this data as elaborated below, and based on this analysis produces output of a bioinformatically detected group of novel genes designated 108.

[0075] Expressed RNA data 102 comprises published expressed sequence tags (EST) data, , published mRNA data, as well as other sources of published RNA data. Sequenced DNA data 104 comprises alphanumeric data describing sequenced genomic data, which preferably includes annotation data such as location of known protein coding regions relative to the sequenced data. Protein function data 106 comprises scientific publications reporting studies which elucidated physiological function known proteins, and their connection, involvement and possible utility in treatment and diagnosis of various diseases. Expressed RNA data 102, sequenced DNA data 104 may preferably be obtained from data published by the National Center for Bioinformatics (NCBI) at the National Institute of Health (NIH), as well as from various other published data sources. Protein function data 106 may preferably be obtained from any one of numerous relevant published data sources, such as the Online Mendelian Inherited Disease In Man (OMIM) database developed by John Hopkins Uni-

versity, and also published by NCBI.

[0076] Prior to actual detection of bioinformatically detected novel genes 108 by the bioinformatic gene detection engine 100, a process of bioinformatic gene detection engine training & validation designated 110 takes place. This process uses the known miRNA genes as a training set (some 200 such genes have been found to date using biological laboratory means), to train the bioinformatic gene detection engine 100 to bioinformatically recognize miRNA-like genes, and their respective potential target binding sites. Bioinformatic gene detection engine training & validation 110 is further describe hereinbelow with reference to Fig. 3.

[0077] The bioinformatic gene detection engine 100 comprises several modules which are preferably activated sequentially, and are described as follows:

[0078] A non-coding genomic sequence detector 112 operative to bioinformatically detect non-protein coding genomic sequences. The non-coding genomic sequence detector 112 is further described hereinbelow with reference to Figs. 4A and 4B.

[0079] A hairpin detector 114 operative to bioinformatically detect genomic "hairpin-shaped" sequences, similar to

VGAM FOLDED PRECURSOR of Fig. 1. The hairpin detector 114 is further described hereinbelow with reference to Figs. 5A and 5B.

[0080] A dicer-cut location detector 116 operative to bioinformatically detect the location on a hairpin shaped sequence which is enzymatically cut by DICER COMPLEX of Fig. 1. The dicer-cut location detector 116 is further described hereinbelow with reference to Fig. 6A.

[0081] A target-gene binding-site detector 118 operative to bioinformatically detect host target having binding sites, the nucleotide sequence of which is partially complementary to that of a given genomic sequence, such as a sequence cut by DICER COMPLEX of Fig. 1. The target-gene binding-site detector 118 is further described hereinbelow with reference to Figs. 7A and 7B.

[0082] A function & utility analyzer 120 operative to analyze function and utility of host target, in order to identify host target which have a significant clinical function and utility. The function & utility analyzer 120 is further described hereinbelow with reference to Fig. 8.

[0083] Hardware implementation of the bioinformatic gene detection engine 100 is important, since significant computing power is preferably required in order to perform the

computation of bioinformatic gene detection engine 100 in reasonable time and cost. As an example, it is estimated that using one powerful 8-processor PC Server, over 30 months of computing time (at 24 hours per day) would be required in order to detect all miRNA genes in human EST data, and their respective binding sites.

[0084] For example, in order to address this challenge at reasonable time and cost, a preferred embodiment of the present invention may comprise a cluster of a large number of personal computers (PCs), such as 100 PCs (Pentium IV, 1.7GHz, with 40GB storage each), connected by Ethernet to several strong servers, such as 4 servers (2-CPU, Xeon 2.2GHz, with 200GB storage each), combined with an 8-processor server (8-CPU, Xeon 550Mhz w/ 8GB RAM) connected via 2 HBA fiber-channels to an EMC Clariion 100-disks, 3.6 Terabyte storage device. Additionally, preferably an efficient database computer program, such as Microsoft (TM) SQL-Server database computer program is used and is optimized to the specific requirements of bioinformatic gene detection engine 100. Furthermore, the PCs are preferably optimized to operate close to 100% CPU usage continuously, as is known in the art. Using suitable hardware and software may preferably

reduce the required calculation time in the abovementioned example from 30 months to 20 days.

[0085] It is appreciated that the abovementioned hardware configuration is not meant to be limiting, and is given as an illustration only. The present invention may be implemented in a wide variety of hardware and software configurations.

[0086] The present invention discloses 15 novel viral genes of the VGAM group of genes, which have been detected bioinformatically, as described hereinbelow with reference to Figs. 15 through 29. Laboratory confirmation of 4 genes of the GAM group of genes is described hereinbelow with reference to Figs. 12 through 14.

[0087] Reference is now made to Fig. 3 which is a simplified flowchart illustrating operation of a mechanism for training of a computer system to recognize the novel genes of the present invention. This mechanism is a preferred implementation of the bioinformatic gene detection engine training & validation 110 described hereinabove with reference to Fig. 2.

[0088] Bioinformatic gene detection engine training & validation 110 of Fig. 2 begins by training the bioinformatic gene detection engine to recognize known miRNA genes, as

designated by numeral 122. This training step comprises hairpin detector training & validation 124, further described hereinbelow with reference to Fig. 12 A, dicer-cut location detector training & validation 126, further described hereinbelow with reference to Fig. 6A and 6B, and target-gene binding-site detector training & validation 128, further described hereinbelow with reference to Fig. 7A.

[0089] Next, the bioinformatic gene detection engine 100 is used to bioinformatically detect sample novel genes, as designated by numeral 130. An example of a sample novel gene thus detected is described hereinbelow with reference to Fig. 12.

[0090] Finally, wet lab experiments are preferably conducted in order to validate expression and preferably function the sample novel genes detected by the bioinformatic gene detection engine 100 in the previous step. An example of wet-lab validation of the abovementioned sample novel gene bioinformatically detected by the system is described hereinbelow with reference to Figs. 13A and 13B.

[0091] Reference is now made to Fig. 4A which is a simplified block diagram of a preferred implementation of the non-coding genomic sequence detector 112 described herein-

above with reference to Fig. 2. Non-protein coding genomic sequence detector 112 of Fig. 2 preferably receives as input at least two types of published genomic data: expressed RNA data 102, including EST data and mRNA data, and sequenced DNA data 104. After its initial training, indicated by numeral 134, and based on the above-mentioned input data, the non-protein coding genomic sequence detector 112 produces as output a plurality of non-protein coding genomic sequences 136. Preferred operation of the non-protein coding genomic sequence detector 112 is described hereinbelow with reference to Fig. 4B.

[0092] Reference is now made to Fig. 4B which is a simplified flowchart illustrating a preferred operation of the non-coding genomic sequence detector 112 of Fig. 2. Detection of non-protein coding genomic sequences to be further analyzed by the system generally preferably progresses in one of the following two paths.

[0093] A first path for detecting non-protein coding genomic sequences begins by receiving a plurality of known RNA sequences, such as EST data. Each RNA sequence is first compared to all known protein-coding sequences, in order to select only those RNA sequences which are non-

protein coding. This can preferably be performed by BLAST comparison of the RNA sequence to known protein coding sequences. The abovementioned BLAST comparison to the DNA preferably also provides the localization of the RNA on the DNA.

[0094] Optionally, an attempt may be made to "expand" the non-protein RNA sequences thus found, by searching for transcription start and end signals, upstream and downstream of location of the RNA on the DNA respectively, as is well known in the art.

[0095] A second path for detecting non-protein coding genomic sequences starts by receiving DNA sequences. The DNA sequences are parsed into non protein coding sequences, based on published DNA annotation data: extracting those DNA sequences which are between known protein coding sequences. Next, transcription start and end signals are sought. If such signals are found, and depending on their "strength", probable expressed non-protein coding genomic sequences are yielded.

[0096] Reference is now made to Fig. 5A which is a simplified block diagram of a preferred implementation of the hairpin detector 114 described hereinabove with reference to Fig. 2.

[0097]   The goal of the hairpin detector 114 is to detect "hairpin" shaped genomic sequences, similar to those of known miRNA genes. As mentioned hereinabove with reference to Fig. 1, a "hairpin" genomic sequence refers to a genomic sequence which "folds onto itself" forming a hairpin like shape, due to the fact that nucleotide sequence of the first half of the nucleotide sequence is an accurate or

[0098]   The hairpin detector 114 of Fig. 2 receives as input a plurality of non-protein coding genomic sequences 136 of Fig. 4A, and after a phase of hairpin detector training & validation 124 of Fig. 3, is operative to detect and output "hairpin shaped" sequences found in the input expressed non-protein coding sequences, designated by numeral 138.

[0099]   The phase of hairpin detector training & validation 124 is an iterative process of applying the hairpin detector 114 to known hairpin shaped miRNA genes, calibrating the hairpin detector 114 such that it identifies the training set of known hairpins, as well as sequences which are similar thereto. Preferred operation of the hairpin detector 114 is described hereinbelow with reference to Fig. 5B.

[0100]   Reference is now made to Fig. 5B which is a simplified flowchart illustrating a preferred operation of the hairpin

detector 114 of Fig. 2.

[0101] A hairpin structure is a two dimensional folding structure, resulting from the nucleotide sequence pattern: the nucleotide sequence of the first half of the hairpin sequence is an inversed-reversed sequence of the second half thereof. Different methodologies are known in the art for detection of various two dimensional and three dimensional hairpin structures.

[0102] In a preferred embodiment of the present invention, the hairpin detector 114 initially calculates possible 2-dimensional (2D) folding patterns of a given one of the non-protein coding genomic sequences 136, preferably using a 2D folding algorithm based on free-energy calculation, such as the Zucker algorithm, as is well known in the art.

[0103] Next, the hairpin detector 114 analyzes the results of the 2D folding, in order to determine the presence, and location of hairpin structures. A 2D folding algorithm typically provides as output a listing of the base-pairing of the 2D folded shape, i.e. a listing of which all two pairs of nucleotides in the sequence which will bond. The goal of this second step, is to asses this base-pairing listing, in order to determine if it describes a hairpin type bonding pat-

tern.

[0104] The hairpin detector 114 then assess those hairpin structures found by the previous step, comparing them to hairpins of known miRNA genes, using various parameters such as length, free-energy, amount and type of mismatches, etc. Only hairpins that bear statistically significant resemblance of the population of hairpins of known miRNAs, according to the abovementioned parameters are accepted.

[0105] Lastly, the hairpin detector 114 attempts to select those hairpin structures which are as stable as the hairpins of know miRNA genes. This may be achieved in various manners. A preferred embodiment of the present invention utilizes the following methodology comprising three steps:

[0106] First, the hairpin detector 114 attempts to group potential hairpins into "families" of closely related hairpins. As is known in the art, a free-energy calculation algorithm, typically provides multiple "versions" each describing a different possible 2D folding pattern for the given genomic sequence, and the free energy of such possible folding. The hairpin detector 114 therefore preferably assesses all hairpins found on all "versions", grouping hairpins which

appear in different versions, but which share near identical locations into a common "family" of hairpins. For example, all hairpins in different versions, the center of which is within 7 nucleotides of each other may preferably be grouped to a single "family".

[0107] Next, hairpin "families" are assessed, in order to select only those families which represent hairpins that are as stable as those of known miRNA hairpins. For example, preferably only families which are represented in at least 65% of the free-energy calculation 2D folding versions, are considered stable.

[0108] Finally, an attempt is made to select the most suitable hairpin from each selected family. For example, preferably the hairpin which appears in more versions than other hairpins, and in versions the free-energy of which is lower, may be selected.

[0109] Reference is now made to Fig. 6A which is a simplified block diagram of a preferred implementation of the dicer-cut location detector 116 described hereinabove with reference to Fig. 2.

[0110] The goal of the dicer-cut location detector 116 is to detect the location in which DICER COMPLEX of Fig. 1, comprising the enzyme Dicer, would "dice" the given hairpin

sequence, similar to VGAM FOLDED PRECURSOR RNA, yielding VGAM RNA both of Fig. 1.

[0111] The dicer-cut location detector 116 of Fig. 2 therefore receives as input a plurality of hairpins on genomic sequences 138 of Fig. 5A, which were calculated by the previous step, and after a phase of dicer-cut location detector training & validation 126 of Fig. 3, is operative to detect a respective plurality of dicer-cut sequences from hairpins 140, one for each hairpin.

[0112] In a preferred embodiment of the present invention, the dicer-cut location detector 116 preferably uses a combination of neural networks, Bayesian networks, Markovian modeling, and Support Vector Machines (SVMs) trained on the known dicer-cut locations of known miRNA genes, in order to detect dicer-cut locations. Dicer-cut location detector training & validation 126, which is further described hereinbelow with reference to Fig. 6B.

[0113] Reference is now made to Fig. 6 B which is a simplified flowchart illustrating a preferred implementation of dicer-cut location detector training & validation 126 of Fig. 3. Dicer-cut location detector 116 first preprocesses known miRNA hairpins and their respective dicer-cut locations, so as to be able to properly analyze them and train the

detection system accordingly:

[0114] The folding pattern is calculated for each known miRNA, preferably based on free-energy calculation, and the size of the hairpin, the size of the loop at the center of the hairpin, and "bulges" (i.e. mismatched base-pairs) in the folded hairpin are noted.

[0115] The dicer-cut location, which is known for known miRNA genes, is noted relative to the above, as well as to the nucleotides in each location along the hairpin. Frequency of identity of nucleotides, and nucleotide-pairing, relative to their location in the hairpin, and relative to the known dicer-cut location in the known miRNA genes is analyzed and modeled.

[0116] Different techniques are well known in the art for analysis of existing pattern from a given "training set" of species belonging to a genus, which techniques are then capable, to a certain degree, to detect similar patterns in other species not belonging to the training-set genus. Such techniques include, but are not limited to neural networks, Bayesian networks, Support Vector Machines (SVM), Genetic Algorithms, Markovian modeling, and others, as is well known in the art.

[0117] Using such techniques, preferably a combination of sev-

eral of the above techniques, the known hairpins are represented as a several different networks (such as neural, Bayesian, or SVM) input and output layers. Both nucleotide, and "bulge" (i.e. nucleotide pairing or mismatch) are represented for each position in the hairpin, at the input layer, and a corresponding true/false flag at each position, indicating whether it was diced by dicer at the output layer. Multiple networks are preferably used concurrently, and the results therefrom are integrated and further optimized. Markovian modeling may also be used to validate the results and enhance their accuracy. Finally, the bioinformatic detection of dicer-cut location of a sample novel is confirmed by wet-lab experimentation.

[0118] Reference is now made to Fig. 7A which is a simplified block diagram of a preferred implementation of the target-gene binding-site detector 118 described hereinabove with reference to Fig. 2. The goal of the target-gene binding-site detector 118 is to detect a BINDING SITE of Fig. 1, located in an untranslated region of the RNA of a known gene, the nucleotide sequence of which BINDING SITE is at least partially complementary to that of a VGAM RNA of Fig. 1, thereby determining that the abovementioned known gene is a target gene of VGAM of

Fig. 1.

[0119]   The target-gene binding-site detector 118 of Fig. 2 therefore receives as input a plurality of dicer-cut sequences from hairpins 140 of Fig. 6A which were calculated by the previous step, and a plurality of potential target gene sequences 142 which derive sequence DNA data 104 of Fig. 2, and after a phase of target-gene binding-site detector training & validation 128 of Fig. 3, is operative to detect target-genes having binding site/s 144 the nucleotide sequence of which is at least partially complementary to that of each of the plurality of dicer-cut sequences from hairpins 140. Preferred operation of the target-gene binding-site detector is further described hereinbelow with reference to Fig. 7B.

[0120]   Reference is now made to Fig. 7B which is a simplified flowchart illustrating a preferred operation of the target-gene binding-site detector 118 of Fig. 2. In a preferred embodiment of the present invention, the target-gene binding-site detector 118 first performs a BLAST comparison of the nucleotide sequence of each of the plurality of dicer-cut sequences from hairpins 140, to the potential target gene sequences 142, in order to find crude potential matches. Blast results are then filtered to results which

are similar to those of known binding sites (e.g. binding sites of miRNA genes Lin-4 and Let-7 to target genes Lin-14, Lin-41, Lin 28 etc.). Next the binding site is expanded, checking if nucleotide sequenced immediately adjacent to the binding site found by BLAST, may improve the match. Suitable binding sites, then are computed for free-energy and spatial structure. The results are analyzed, selecting only those binding sites, which have free-energy and spatial structure similar to that of known binding sites.

[0121] Reference is now made to Fig. 8 which is a simplified flowchart illustrating a preferred operation of the function & utility analyzer 120 described hereinabove with reference to Fig. 2. The goal of the function & utility analyzer 120 is to determine if a potential target gene is in fact a valid clinically useful target gene. Since a potential novel VGAM gene binding a binding site in the UTR of a target gene is understood to inhibit expression of that target gene, and if that target gene is shown to have a valid clinical utility, then in such a case it follows that the potential novel gene itself also has a valid useful function which is the opposite of that of the target gene.

[0122] The function & utility analyzer 120 preferably receives as

input a plurality of potential novel target genes having binding-site/s 144, generated by the target-gene binding-site detector 118, both of Fig. 7A. Each potential gene, is evaluated as follows:

[0123] First the system first checks to see if the function of the potential target gene is scientifically well established. Preferably, this can be achieved bioinformatically by searching various published data sources presenting information on known function of proteins. Many such data sources exist and are published as is well known in the art.

[0124] Next, for those target genes the function of which is scientifically known and is well documented, the system then checks if scientific research data exists which links them to known diseases. For example, a preferred embodiment of the present invention utilizes the OMIM(TM) database published by NCBI, which summarizes research publications relating to genes which have been shown to be associated with diseases.

[0125] Finally, the specific possible utility of the target gene is evaluated. While this process too may be facilitated by bioinformatic means, it might require human evaluation of published scientific research regarding the target gene, in

order to determine the utility of the target gene to the diagnosis and or treatment of specific disease. Only potential novel genes, the target-genes of which have passed all three examinations, are accepted as novel genes.

[0126] Reference is now made to Fig. 9, which is a simplified diagram describing a novel bioinformatically detected group of regulatory genes, referred to here as Genomic Record (GR) genes, that encode an "operon-like" cluster of novel miRNA-like genes, each modulating expression of a plurality of host target, the function and utility of which target genes is known.

[0127] GR GENE (Genomic Record Gene) is gene of a novel, bioinformatically detected group of regulatory, non protein coding, RNA genes. The method by which GR is detected is described hereinabove with reference to FIGS. 6-15.

[0128] GR GENE encodes an RNA molecule, typically several hundred nucleotides long, designated GR PRECURSOR RNA.

[0129] GR PRECURSOR RNA folds spatially, as illustrated by GR FOLDED PRECURSOR RNA, into a plurality of what is known in the art as "hair-pin" structures. The nucleotide sequence of GR PRECURSOR RNA comprises a plurality of segments, the first half of each such segment having a nucleotide sequence which is at least a partial inversed-

reversed sequence of the second half thereof, thereby causing formation of a plurality of "hairpin" structures, as is well known in the art.

[0130] GR FOLDED PRECURSOR RNA is naturally processed by cellular enzymatic activity, into 3 separate hairpin shaped RNA segments, each corresponding to VGAM PRECURSOR RNA of Fig. 1, designated VGAM1 PRECURSOR, VGAM2 PRECURSOR and VGAM3 PRECURSOR respectively.

[0131] The above mentioned VGAM precursors, are diced by Dicer of FIG. 1, yielding short RNA segments of about 22 nucleotides in length, each corresponding to VGAM RNA of FIG. 1, designated VGAM1, VGAM2 and VGAM3 respectively.

[0132] VGAM1, VGAM2 and VGAM3 each bind complementarily to binding sites located in untranslated regions of respective host target, designated VGAM1-TARGET RNA, VGAM2-TARGET RNA and VGAM3-TARGET RNA respectively. This binding inhibits translation of the respective target proteins designated VGAM1-TARGET PROTEIN, VGAM2-TARGET PROTEIN and VGAM3-TARGET PROTEIN respectively.

[0133] The structure of VGAM genes comprised in a GR GENE, and their mode of modulation of expression of their re-

spective target genes is described hereinabove with reference to Fig. 1. The bioinformatic approach to detection of VGAM genes comprised in a GR GENE is described hereinabove with reference to Figs. 9 through 14.

[0134] The present invention discloses 17 novel viral genes of the GR group of genes, which have been detected bioinformatically, as described hereinbelow with reference to Figs. 15 through 31. Laboratory confirmation of 3 genes of the GR group of genes is described hereinbelow with reference to Figs. 9A through 14.

[0135] In summary, the current invention discloses a very large number of novel viral GR genes, each of which encodes a plurality of VGAM genes, which in turn may modulate expression of a plurality of host target proteins.

[0136] Reference is now made to Fig. 10 which is a block diagram illustrating different utilities of genes of the novel group of genes of the present invention referred to here as VGAM genes and GR genes.

[0137] The present invention discloses a first plurality of novel genes referred to here as VGAM genes, and a second plurality of operon-like genes referred to here as GR genes, each of the GR genes encoding a plurality of VGAM genes. The present invention further discloses a very large num-

ber of known target-genes, which are bound by, and the expression of which is modulated by each of the novel genes of the present invention. Published scientific data referenced by the present invention provides specific, substantial, and credible evidence that the abovementioned target genes modulated by novel genes of the present invention, are associated with various diseases. Specific novel genes of the present invention, target genes thereof and diseases associated therewith, are described hereinbelow with reference to Figs. 15 through 29 It is therefore appreciated that a function of VGAM genes and GR genes of the present invention is modulation of expression of target genes related to known diseases, and that therefore utilities of novel genes of the present invention include diagnosis and treatment of the abovementioned diseases. Fig. 10 describes various types of diagnostic and therapeutic utilities of novel genes of the present invention.

[0138] A utility of novel genes of the present invention is detection of VGAM genes and of GR genes. It is appreciated that since VGAM genes and GR genes modulate expression of disease related target genes, that detection of expression of VGAM genes in clinical scenarios associated

with said diseases is a specific, substantial and credible utility. Diagnosis of novel genes of the present invention may preferably be implemented by RNA expression detection techniques, including but not limited to biochips, as is well known in the art. Diagnosis of expression of genes of the present invention may be useful for research purposes, in order to further understand the connection between the novel genes of the present invention and the abovementioned related diseases, for disease diagnosis and prevention purposes, and for monitoring disease progress.

[0139] Another utility of novel genes of the present invention is anti-VGAM gene therapy, a mode of therapy which allows up regulation of a disease related target-gene of a novel VGAM gene of the present invention, by lowering levels of the novel VGAM gene which naturally inhibits expression of that target gene. This mode of therapy is particularly useful with respect to target genes which have been shown to be under-expressed in association with a specific disease. Anti-VGAM gene therapy is further discussed hereinbelow with reference to Figs. 11A and 11B.

[0140] A further utility of novel genes of the present invention is VGAM replacement therapy, a mode of therapy which

achieves down regulation of a disease related target-gene of a novel VGAM gene of the present invention, by raising levels of the VGAM gene which naturally inhibits expression of that target gene. This mode of therapy is particularly useful with respect to target genes which have been shown to be over-expressed in association with a specific disease. VGAM replacement therapy involves introduction of supplementary VGAM gene products into a cell, or stimulation of a cell to produce excess VGAM gene products. VGAM replacement therapy may preferably be achieved by transfecting cells with an artificial DNA molecule encoding a VGAM gene, which causes the cells to produce the VGAM gene product, as is well known in the art.

[0141] Yet a further utility of novel genes of the present invention is modified VGAM therapy. Disease conditions are likely to exist, in which a mutation in a binding site of a VGAM gene prevents natural VGAM gene to effectively bind inhibit a disease related target-gene, causing up regulation of that target gene, and thereby contributing to the disease pathology. In such conditions, a modified VGAM gene is designed which effectively binds the mutated VGAM binding site, i.e. is an effective anti-sense of the

mutated VGAM binding site, and is introduced in disease effected cells. Modified VGAM therapy is preferably achieved by transfecting cells with an artificial DNA molecule encoding the modified VGAM gene, which causes the cells to produce the modified VGAM gene product, as is well known in the art.

[0142] An additional utility of novel genes of the present invention is induced cellular differentiation therapy. As aspect of the present invention is finding genes which determine cellular differentiation, as described hereinabove with reference to Fig. 11. Induced cellular differentiation therapy comprises transfection of cell with such VGAM genes thereby determining their differentiation as desired. It is appreciated that this approach may be widely applicable, inter alia as a means for auto transplantation harvesting cells of one cell-type from a patient, modifying their differentiation as desired, and then transplanting them back into the patient. It is further appreciated that this approach may also be utilized to modify cell differentiation in vivo, by transfecting cells in a genetically diseased tissue with a cell-differentiation determining VGAM gene, thus stimulating these cells to differentiate appropriately.

[0143] Reference is now made to Figs. 11A and 11B, simplified

diagrams which when taken together illustrate anti-VGAM gene therapy mentioned hereinabove with reference to Fig. 10. A utility of novel genes of the present invention is anti-VGAM gene therapy, a mode of therapy which allows up regulation of a disease related target-gene of a novel VGAM gene of the present invention, by lowering levels of the novel VGAM gene which naturally inhibits expression of that target gene. Fig. 11A shows a normal VGAM gene, inhibiting translation of a target gene of VGAM gene, by binding to a BINDING SITE found in an untranslated region of TARGET RNA, as described hereinabove with reference to Fig. 1.

[0144] Fig. 11B shows an example of anti-VGAM gene therapy. ANTI-VGAM RNA is short artificial RNA molecule the sequence of which is an anti-sense of VGAM RNA. Anti-VGAM treatment comprises transfecting diseased cells with ANTI-VGAM RNA, or with a DNA encoding thereof. The ANTI-VGAM RNA binds the natural VGAM RNA, thereby preventing binding of natural VGAM RNA to its BINDING SITE. This prevents natural translation inhibition of TARGET RNA by VGAM RNA, thereby up regulating expression of TARGET PROTEIN.

[0145] It is appreciated that anti-VGAM gene therapy is particu-

larly useful with respect to target genes which have been shown to be under-expressed in association with a specific disease.

[0146] Reference is now made to Fig. 12A which is an annotated sequence of an EST comprising a novel gene detected by the gene detection system of the present invention. Fig. 12A shows the nucleotide sequence of a known human non-protein coding EST (Expressed Sequence Tag), identified as EST72223. It is appreciated that the sequence of this EST comprises sequences of one known miRNA gene, identified as MIR98, and of one novel GAM gene, referred to here as GAM24, detected by the bioinformatic gene detection system of the present invention, described hereinabove with reference to Fig. 2.

[0147] Reference is now made to Figs. 12B and 12C that are pictures of laboratory results, which when taken together demonstrate laboratory confirmation of expression of the bioinformatically detected novel gene of Fig. 12A. Reference is now made to Fig. 12B which is a Northern blot analysis of MIR-98 and EST72223 transcripts. MIR-98 and EST72223 were reacted with MIR-98 and GAM24 probes as indicated in the figure. It is appreciated that the probes of both MIR-98 and GAM24 reacted with EST72223, indi-

cating that EST72223 contains the sequences of MIR-98 and of GAM24. It is further appreciated that the probe of GAM24 does not cross-react with MIR-98.

[0148] Reference is now made to Fig. 12C. A Northern blot analysis of EST72223 and MIR-98 transfections were performed, subsequently marking RNA by the MIR-98 and GAM24 probes . Left, Northern reacted with MIR-98, Right, Northern reacted with GAM24. The molecular Sizes of EST72223, MIR-98 and GAM24 are indicated by arrows. Hela are control cells that have not been introduced to exogenous RNA. EST and MIR-98 Transfections are RNA obtained from Hela transfected with EST72223 and MIR-98, respectively. MIR-98 and EST are the transcripts used for the transfection experiment. The results indicate that EST72223, when transfected into Hela cells, is cut yielding known miRNA gene MIR-98 and novel miRNA gene GAM24.

[0149] Reference is now made to Fig. 12D, which is a Northern blot of a lisate experiment with MIR-98 and GAM24. Northern blot analysis of hairpins in EST72223 . Left, Northern reacted with predicted Mir-98 hairpin probe, Right, Northern reacted with predicted GAM24 hairpin probe. The molecular size of EST Is indicated by arrow.

The molecular sizes of Mir-98 and GAM24 are 80nt and 100nt, respectively as indicated by arrows. The 22nt molecular marker is indicated by arrow. 1-Hela lysate; 2-EST incubated 4h with Hela lysate; 3-EST without lysate; 4-Mir transcript incubated 4h with Hela lysate; 5-Mir transcript incubated overnight with Hela lysate; 6- Mir transcript without lysate; 7-RNA extracted from Hela cells following transfection with Mir transcript.

[0150] Technical methods used in experiments, the results of which are depicted in Figs. 12B, 12C and 12D are as follows:

[0151] *Transcript preparations:* Digoxigenin (DIG) labeled transcripts were prepared from EST72223 (TIGER), MIR98 and predicted precursor hairpins by using a DIG RNA labeling kit (Roche Molecular Biochemicals) according to the manufacture"s protocol. Briefly, PCR products with T7 promoter at the 5" end or T3 promoter at the 3"end were prepared from each DNA in order to use it as a template to prepare sense and antisense transcripts, respectively. MIR-98 was amplified using EST72223 as a templet with T7miR98 forward primer:

5-"TAATACGACTCACTATAGGGTGAGGTAGTAAGTTGTATT GTT-3"and T3miR98 revse primer:

5"-AATTAACCCTCACTAAAGGGAAAGTAGTAAGTTGTATAG TT-3"EST72223 was amplified with T7-EST 72223 forward primer:5"-TAATACGACTCACTATAGGCCCTTATTAGAGGAT TCTGCT-3"and T3-EST72223 reverse primer:5"-AATTAACCCTCACTAAAGGTTTTTTTTTCCTGAG ACAGAGT-3" Bet-4 was amplified using EST72223 as a templet with Bet-4 forward primer: 5"-GAGGCAGGAGAATTGCTTGA- 3" and T3-EST72223 re-verse primer:5"-AATTAACCCTCACTAAAGGCCTGAGACAGAGTCT TGCTC-3"The PCR products were cleaned and used for DIG-labeled or unlabeled transcription reactions with the appropriate polymerase. For transfection experiments, CAP reaction was performed by using a mMassage mMa-chine kit (Ambion).

[0152] *Transfection procedure:*Transfection of Hela cells was per-formed by using TransMessenger reagent (Qiagen) ac-cording to the manufacture"s protocol. Briefly, Hela cells were seeded to 1-2x 10^6 cells per plate a day before transfection. Two µg RNA transcripts were mixed with 8µl Enhancer in a final volume of 100µl, mixed and incubated at room temperature for 5 min. 16µl TransMessenger reagent was added to the RNA-Enhancer, mixed and incu-

bated for additional 10 min. Cell plates were washed with sterile PBS twice and then incubated with the transfection mix diluted with 2.5 ml DMEM medium without serum. Cells were incubated with transfection mix for three hours under their normal growth condition (370C and 5% CO2) before the transfection mix was removed and a fresh DMEM medium containing serum was added to the cells. Cells were left to grow 48 hours before harvesting.

[0153] *Target RNA cleavage assay:* Cap-labeled target RNAs were generated using mMessage mMachine^{TM} (Ambion). Caped RNA transcripts were preincubated at 30^{0}C for 15 min in supplemented Hela S100 obtained from Computer Cell Culture, Mos, Belgium. After addition of all components, final concentrations were 100mM target RNA, 1m M ATP, 0.2mM GTP, 10U/ml RNasin, 30μg/ml creatine kinase, 25mM creatine phosphate, and 50% S100 extract. Incubation was continued for 4 hours to overnight. Cleavage reaction was stopped by the addition of 8 volumes of proteinase K buffer (200Mm Tris-Hcl, pH 7.5, 25m M EDTA, 300mM NaCl, and 2% SDS). Proteinase K, dissolved in 50mM Tris-HCl, pH 8, 5m M CaCl2, and 50% glycerol, was added to a final concentration of 0.6 mg/ml. Sample were subjected to phenol/chlorophorm extraction and kept

frozen until analyzed by urea-TBE PAGE.

[0154] *Northern analysis:* RNAs were extracted from cells by using Tri-reagent according to the manufacture"s protocol. The RNAs were dissolved in water and heated to 650C to disrupt any association of the 25nt RNA with larger RNA molecules. RNA were placed on ice and incubated for 30 min with PEG (MW=8000) in a final concentration of 5% and NaCl in a final concentration of 0.5M to precipitate high molecular weight nucleic acid. The RNAs were centrifuged at 10,000xg for 10 min to pellet the high molecular weight nucleic acid. The supernatant containing the low molecular weight RNAs was collected and three volumes of ethanol was added. The RNAs were placed at −200C for at least two hours and then centrifuged at 10,000xg for 10 min. The pellets were dissolved in Urea-TBE buffer (1Xtbe, 7M urea) for further analysis by a Northern blot.

[0155] RNA samples were boiled for 5 min before loading on 15%-8% polyacrylamide (19:1) gels containing 7M urea and 1xTBE. Gels were run in 1xTBE at a constant voltage of 300V and then transferred into a nylon membrane. The membrane was exposed to 3min ultraviolet light to cross link the RNAs to the membrane. Hybridization was per-

formed overnight with DIG-labeled probes at 420C. Mem-
branes were washed twice with SSCx2 and 0.2% SDS for 10
min. at 420C and then washed twice with SSCx0.5 for 5
min at room temperature. The membrane was then devel-
oped by using a DIG luminescent detection kit (Roche) us-
ing anti DIG and CSPD reaction, according to the manu-
facture"s protocol.

[0156] It is appreciated that the data presented in Figs. 12A, 12B,
12C and 12D, when taken together validate the function
of the bioinformatic gene detection engine 100 of Fig. 2.
Fig. 12A shows a novel GAM gene bioinformatically de-
tected by the bioinformatic gene detection engine 100,
and Figs. 12B, 12C and 12D show laboratory confirmation
of the expression of this novel gene. This is in accord with
the engine training and validation methodology described
hereinabove with reference to Fig. 3.

[0157] Reference is now made to Fig. 13A which is an annotated
sequence of an EST comprising a novel gene detected by
the gene detection system of the present invention. Fig.
13A shows the nucleotide sequence of a known human
non-protein coding EST (Expressed Sequence Tag), identi-
fied as EST 7929020. It is appreciated that the sequence
of this EST comprises sequences of two novel GAM genes,

referred to here as GAM23 and GAM25, detected by the bioinformatic gene detection system of the present invention, described hereinabove with reference to Fig. 2.

[0158] Reference is now made to Fig. 13B which presents pictures of laboratory results, that demonstrate laboratory confirmation of expression of the bioinformatically detected novel gene of Fig. 13A. Northern blot analysis of hairpins in EST7929020. Left, Northern reacted with predicted GAM25 hairpin probe, Right, Northern reacted with predicted GAM23 hairpin probe. The molecular size of EST is indicated by arrow. The molecular sizes of GAM23 and GAM25 are 60nt, as indicated by arrow. The 22nt molecular marker is indicated by arrow. 1–Hela lysate; 2– EST incubated 4h with Hela lysate ; 3– EST incubated overnight with Hela lysate; 4–EST without lysate; 5–GAM transcript; 6– GAM 22nt marker;7–GAM PCR probe; 8–RNA from control Hela cells; 9–RNA extracted from Hela cells following transfection with EST.

[0159] Reference is now made to Fig. 13C which is a picture of a Northern blot confirming Endogenous expression of bioinformatically detected gene GAM25 of Fig. 13A from in Hela cells. Northern was reacted with a predicted GAM25 hairpin probe. The molecular size of EST7929020

is indicated. The molecular sizes of GAM25 is 58nt, as indicated. A 19nt DNA oligo molecular marker is indicated. Endogenous expression of GAM25 in Hela total RNA fraction and in S-100 fraction is indicated by arrows. 1-GAM25 transcript; 2- GAM25 DNA oligo marker; 3-RNA from control Hela cells; 4-RNA extracted from Hela cells following transfection with EST; 5- RNA extracted from S-100 Hela lysate.

[0160] Reference is now made to Fig. 14A which is an annotated sequence of an EST comprising a novel gene detected by the gene detection system of the present invention. Fig. 14A shows the nucleotide sequence of a known human non-protein coding EST (Expressed Sequence Tag), identified as EST 1388749. It is appreciated that the sequence of this EST comprises sequence of a novel GAM gene, referred to here as GAM26, detected by the bioinformatic gene detection system of the present invention, described hereinabove with reference to Fig. 2.

[0161] Reference is now made to Fig. 14B which is a picture of Northern blot analysis, confirming expression of novel bioinformatically detected gene GAM26, and natural processing thereof from EST1388749. Northern reacted with predicted GAM26 hairpin probe. The molecular size of EST

is indicated by arrow. The molecular sizes of GAM26 is 130nt, as indicated by arrow. The 22nt molecular marker is indicated by arrow. 1-Hela lysate; 2-EST incubated 4h with Hela lysate; 3- EST incubated overnight with Hela lysate; 4-EST without lysate; 5-GAM transcript; 6- GAM 22nt marker; 7-GAM PCR probe.

[0162] Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 15 (VGAM15) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0163] VGAM15 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM15 was detected is described hereinabove with reference to Figs. 2-8.

[0164] VGAM15 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM15 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0165] VGAM15 gene, herein designated VGAM GENE, encodes a VGAM15 precursor RNA, herein designated VGAM PRE-

CURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM15 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM15 precursor RNA is designated SEQ ID:1, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:1 is located at position 7156 relative to the genome of Human immunodeficiency virus 1.

[0166] VGAM15 precursor RNA, herein designated VGAM PRECURSOR RNA, folds onto itself, forming VGAM15 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0167] An enzyme complex designated DICER COMPLEX, dices the VGAM15 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM15 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 7200%) nucleotide sequence of VGAM15 RNA is designated SEQ ID:16, and is provided hereinbelow with reference to the sequence list-ing part.

[0168] VGAM15 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM15 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM15 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untrans-lated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR re-spectively.

[0169] VGAM15 RNA, herein designated VGAM RNA, binds com-plementarily to one or more host target binding sites lo-cated in untranslated regions of VGAM15 host target RNA, herein designated VGAM HOST TARGET RNA. This com-plementary binding is due to the fact that the nucleotide sequence of VGAM15 RNA, herein designated VGAM RNA,

is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM15 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM15 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0170]   The complementary binding of VGAM15 RNA, herein designated VGAM RNA, to host target binding sites on VGAM15 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM15 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM15 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is

therefore outlined by a broken line.

[0171] It is appreciated that VGAM15 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM15 host target genes. The mRNA of each one of this plurality of VGAM15 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-plementary to VGAM15 RNA, herein designated VGAM RNA, and which when bound by VGAM15 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM15 host target proteins.

[0172] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM15 gene, herein designated VGAM GENE, on one or more VGAM15 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression

of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0173] It is yet further appreciated that a function of VGAM15 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM15 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM15 correlate with, and may be deduced from, the identity of the host target genes which VGAM15 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0174] Nucleotide sequences of the VGAM15 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM15 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM15 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM15 are further described hereinbelow with reference to Table 1.

[0175] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM15 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0176] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 16 (VGAM16) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0177] VGAM16 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM16 was detected is described hereinabove with reference to Figs. 2-8.

[0178] VGAM16 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM16 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0179] VGAM16 gene, herein designated VGAM GENE, encodes a VGAM16 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM16 precursor RNA, herein des-

ignated VGAM PRECURSOR RNA, does not encode a pro-
tein. A nucleotide sequence identical or highly similar to
the nucleotide sequence of VGAM16 precursor RNA is
designated SEQ ID:2, and is provided hereinbelow with
reference to the sequence listing part. Nucleotide se-
quence SEQ ID:2 is located at position 4668 relative to the
genome of Human immunodeficiency virus 1.

[0180] VGAM16 precursor RNA, herein designated VGAM PRE-
CURSOR RNA, folds onto itself, forming VGAM16 folded
precursor RNA, herein designated VGAM FOLDED PRECUR-
SOR RNA, which has a two-dimensional hairpin structure.
As is well known in the art, this hairpin structure, is typi-
cal of RNA encoded by miRNA genes, and is due to the
fact that the nucleotide sequence of the first half of the
RNA encoded by a miRNA gene is an accurate or partial
inversed-reversed sequence of the nucleotide sequence of
the second half thereof.

[0181] An enzyme complex designated DICER COMPLEX, dices
the VGAM16 folded precursor RNA, herein designated
VGAM FOLDED PRECURSOR RNA, into VGAM16 RNA,
herein designated VGAM RNA, a single stranded ~22 nt
long RNA segment. As is known in the art, dicing of a
hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 7900%) nucleotide sequence of VGAM16 RNA is designated SEQ ID:17, and is provided hereinbelow with reference to the sequence listing part.

[0182] VGAM16 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM16 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM16 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0183] VGAM16 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM16 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM16 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding

sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM16 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM16 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0184] The complementary binding of VGAM16 RNA, herein designated VGAM RNA, to host target binding sites on VGAM16 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM16 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM16 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0185] It is appreciated that VGAM16 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM16 host target genes. The mRNA of each one of this plurality of VGAM16 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM16 RNA, herein designated VGAM RNA, and which when bound by VGAM16 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM16 host target proteins.

[0186] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM16 gene, herein designated VGAM GENE, on one or more VGAM16 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA

genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0187] It is yet further appreciated that a function of VGAM16 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM16 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM16 correlate with, and may be deduced from, the identity of the host target genes which VGAM16 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0188] Nucleotide sequences of the VGAM16 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM16 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM16 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM16 are further described hereinbelow with reference to Table 1.

[0189] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites

to VGAM16 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0190] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 17 (VGAM17) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0191] VGAM17 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM17 was detected is described hereinabove with reference to Figs. 2-8.

[0192] VGAM17 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM17 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0193] VGAM17 gene, herein designated VGAM GENE, encodes a VGAM17 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM17 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to

the nucleotide sequence of VGAM17 precursor RNA is designated SEQ ID:3, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:3 is located at position 5919 relative to the genome of Human immunodeficiency virus 1.

[0194] VGAM17 precursor RNA, herein designated VGAM PRECURSOR RNA, folds onto itself, forming VGAM17 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0195] An enzyme complex designated DICER COMPLEX, dices the VGAM17 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM17 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 8400%) nucleotide sequence of VGAM17 RNA is designated SEQ ID:18, and is provided hereinbelow with reference to the sequence listing part.

[0196] VGAM17 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM17 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM17 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0197] VGAM17 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM17 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM17 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II

and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM17 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM17 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0198] The complementary binding of VGAM17 RNA, herein designated VGAM RNA, to host target binding sites on VGAM17 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM17 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM17 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0199] It is appreciated that VGAM17 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM17 host target genes. The mRNA of

each one of this plurality of VGAM17 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM17 RNA, herein designated VGAM RNA, and which when bound by VGAM17 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM17 host target proteins.

[0200] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM17 gene, herein designated VGAM GENE, on one or more VGAM17 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0201]   It is yet further appreciated that a function of VGAM17 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM17 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM17 correlate with, and may be deduced from, the identity of the host target genes which VGAM17 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0202]   Nucleotide sequences of the VGAM17 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM17 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM17 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM17 are further described hereinbelow with reference to Table 1.

[0203]   Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM17 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0204] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 18 (VGAM18) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0205] VGAM18 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM18 was detected is described hereinabove with reference to Figs. 2–8.

[0206] VGAM18 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM18 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0207] VGAM18 gene, herein designated VGAM GENE, encodes a VGAM18 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM18 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM18 precursor RNA is designated SEQ ID:4, and is provided hereinbelow with

reference to the sequence listing part. Nucleotide sequence SEQ ID:4 is located at position 1459 relative to the genome of Human immunodeficiency virus 1.

[0208] VGAM18 precursor RNA, herein designated VGAM PRECURSOR RNA, folds onto itself, forming VGAM18 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0209] An enzyme complex designated DICER COMPLEX, dices the VGAM18 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM18 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 7200%) nucleotide sequence of VGAM18 RNA is designated SEQ ID:19, and is

provided hereinbelow with reference to the sequence listing part.

[0210]   VGAM18 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM18 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM18 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0211]   VGAM18 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM18 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM18 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting VGAM18 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM18 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0212] The complementary binding of VGAM18 RNA, herein designated VGAM RNA, to host target binding sites on VGAM18 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM18 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM18 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0213] It is appreciated that VGAM18 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM18 host target genes. The mRNA of each one of this plurality of VGAM18 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM18 RNA, herein designated VGAM RNA, and which when bound by VGAM18 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM18 host target proteins.

[0214] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM18 gene, herein designated VGAM GENE, on one or more VGAM18 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0215] It is yet further appreciated that a function of VGAM18 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM18 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM18 correlate with, and may be deduced from, the identity of the host target genes which VGAM18 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0216] Nucleotide sequences of the VGAM18 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM18 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM18 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM18 are further described hereinbelow with reference to Table 1.

[0217] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM18 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0218] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present

invention, referred to here as Viral Genomic Address Messenger 19 (VGAM19) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0219] VGAM19 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM19 was detected is described hereinabove with reference to Figs. 2-8.

[0220] VGAM19 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM19 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0221] VGAM19 gene, herein designated VGAM GENE, encodes a VGAM19 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM19 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM19 precursor RNA is designated SEQ ID:5, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:5 is located at position 2168 relative to the

genome of Human immunodeficiency virus 1.

[0222] VGAM19 precursor RNA, herein designated VGAM PRE-CURSOR RNA, folds onto itself, forming VGAM19 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0223] An enzyme complex designated DICER COMPLEX, dices the VGAM19 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM19 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 6000%) nucleotide sequence of VGAM19 RNA is designated SEQ ID:20, and is provided hereinbelow with reference to the sequence listing part.

[0224] VGAM19 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM19 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM19 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0225] VGAM19 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM19 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM19 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM19 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM19 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0226] The complementary binding of VGAM19 RNA, herein designated VGAM RNA, to host target binding sites on VGAM19 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM19 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM19 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0227] It is appreciated that VGAM19 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM19 host target genes. The mRNA of each one of this plurality of VGAM19 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM19 RNA, herein designated VGAM

RNA, and which when bound by VGAM19 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM19 host target proteins.

[0228] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM19 gene, herein designated VGAM GENE, on one or more VGAM19 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0229] It is yet further appreciated that a function of VGAM19 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM19 include diagnosis, prevention and

treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM19 correlate with, and may be deduced from, the identity of the host target genes which VGAM19 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0230] Nucleotide sequences of the VGAM19 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM19 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM19 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM19 are further described hereinbelow with reference to Table 1.

[0231] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM19 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0232] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 20 (VGAM20) viral gene, which modulates expres-

sion of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0233] VGAM20 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM20 was detected is described hereinabove with reference to Figs. 2-8.

[0234] VGAM20 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM20 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0235] VGAM20 gene, herein designated VGAM GENE, encodes a VGAM20 precursor RNA, herein designated VGAM PRE-CURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM20 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM20 precursor RNA is designated SEQ ID:6, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:6 is located at position 587 relative to the genome of Human immunodeficiency virus 1.

[0236] VGAM20 precursor RNA, herein designated VGAM PRE-

CURSOR RNA, folds onto itself, forming VGAM20 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0237] An enzyme complex designated DICER COMPLEX, dices the VGAM20 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM20 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 8400%) nucleotide sequence of VGAM20 RNA is designated SEQ ID:21, and is provided hereinbelow with reference to the sequence listing part.

[0238] VGAM20 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA,

VGAM20 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM20 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0239] VGAM20 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM20 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM20 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM20 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM20 host target RNA, herein

designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0240] The complementary binding of VGAM20 RNA, herein designated VGAM RNA, to host target binding sites on VGAM20 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM20 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM20 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0241] It is appreciated that VGAM20 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM20 host target genes. The mRNA of each one of this plurality of VGAM20 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM20 RNA, herein designated VGAM RNA, and which when bound by VGAM20 RNA, herein designated VGAM RNA, causes inhibition of translation of

respective one or more VGAM20 host target proteins.

[0242] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM20 gene, herein designated VGAM GENE, on one or more VGAM20 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0243] It is yet further appreciated that a function of VGAM20 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM20 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of

VGAM20 correlate with, and may be deduced from, the identity of the host target genes which VGAM20 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0244] Nucleotide sequences of the VGAM20 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM20 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM20 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM20 are further described hereinbelow with reference to Table 1.

[0245] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM20 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0246] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 21 (VGAM21) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0247] VGAM21 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM21 was detected is described hereinabove with reference to Figs. 2-8.

[0248] VGAM21 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM21 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0249] VGAM21 gene, herein designated VGAM GENE, encodes a VGAM21 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM21 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM21 precursor RNA is designated SEQ ID:7, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:7 is located at position 7857 relative to the genome of Human immunodeficiency virus 1.

[0250] VGAM21 precursor RNA, herein designated VGAM PRE-CURSOR RNA, folds onto itself, forming VGAM21 folded precursor RNA, herein designated VGAM FOLDED PRECUR-

SOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0251] An enzyme complex designated DICER COMPLEX, dices the VGAM21 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM21 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 7700%) nucleotide sequence of VGAM21 RNA is designated SEQ ID:22, and is provided hereinbelow with reference to the sequence listing part.

[0252] VGAM21 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM21 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM21 host target RNA, herein designated

VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0253] VGAM21 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM21 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM21 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM21 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM21 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in

the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0254] The complementary binding of VGAM21 RNA, herein designated VGAM RNA, to host target binding sites on VGAM21 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM21 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM21 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0255] It is appreciated that VGAM21 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM21 host target genes. The mRNA of each one of this plurality of VGAM21 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM21 RNA, herein designated VGAM RNA, and which when bound by VGAM21 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM21 host target proteins.

[0256] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM21 gene, herein designated VGAM GENE, on one or more VGAM21 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0257] It is yet further appreciated that a function of VGAM21 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM21 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM21 correlate with, and may be deduced from, the identity of the host target genes which VGAM21 binds and

inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0258] Nucleotide sequences of the VGAM21 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM21 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM21 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM21 are further described hereinbelow with reference to Table 1.

[0259] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM21 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0260] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 22 (VGAM22) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0261] VGAM22 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM22 was detected is described hereinabove with reference to Figs. 2-8.

[0262] VGAM22 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM22 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0263] VGAM22 gene, herein designated VGAM GENE, encodes a VGAM22 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM22 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM22 precursor RNA is designated SEQ ID:8, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:8 is located at position 8292 relative to the genome of Human immunodeficiency virus 1.

[0264] VGAM22 precursor RNA, herein designated VGAM PRECURSOR RNA, folds onto itself, forming VGAM22 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typi-

cal of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0265] An enzyme complex designated DICER COMPLEX, dices the VGAM22 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM22 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 7600%) nucleotide sequence of VGAM22 RNA is designated SEQ ID:23, and is provided hereinbelow with reference to the sequence listing part.

[0266] VGAM22 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM22 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM22 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untrans-

lated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0267] VGAM22 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM22 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM22 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM22 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM22 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR re-

gion, the 5UTR region, or in both 3UTR and 5UTR regions.

[0268] The complementary binding of VGAM22 RNA, herein designated VGAM RNA, to host target binding sites on VGAM22 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM22 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM22 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0269] It is appreciated that VGAM22 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM22 host target genes. The mRNA of each one of this plurality of VGAM22 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM22 RNA, herein designated VGAM RNA, and which when bound by VGAM22 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM22 host target proteins.

[0270] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM22 gene, herein designated VGAM GENE, on one or more VGAM22 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0271] It is yet further appreciated that a function of VGAM22 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM22 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM22 correlate with, and may be deduced from, the identity of the host target genes which VGAM22 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0272] Nucleotide sequences of the VGAM22 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM22 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM22 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM22 are further described hereinbelow with reference to Table 1.

[0273] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM22 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0274] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 23 (VGAM23) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0275] VGAM23 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM23 was detected is described hereinabove with reference to Figs. 2-8.

[0276] VGAM23 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM23 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0277] VGAM23 gene, herein designated VGAM GENE, encodes a VGAM23 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM23 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM23 precursor RNA is designated SEQ ID:9, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:9 is located at position 5531 relative to the genome of Human immunodeficiency virus 1.

[0278] VGAM23 precursor RNA, herein designated VGAM PRECURSOR RNA, folds onto itself, forming VGAM23 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the

RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0279] An enzyme complex designated DICER COMPLEX, dices the VGAM23 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM23 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 6900%) nucleotide sequence of VGAM23 RNA is designated SEQ ID:24, and is provided hereinbelow with reference to the sequence listing part.

[0280] VGAM23 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM23 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM23 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR re-

spectively.

[0281]   VGAM23 RNA, herein designated VGAM RNA, binds com-
plementarily to one or more host target binding sites lo-
cated in untranslated regions of VGAM23 host target RNA,
herein designated VGAM HOST TARGET RNA. This com-
plementary binding is due to the fact that the nucleotide
sequence of VGAM23 RNA, herein designated VGAM RNA,
is an accurate or a partial inversed-reversed sequence of
the nucleotide sequence of each of the host target binding
sites. As an illustration, Fig. 1 shows 3 such host target
binding sites, designated BINDING SITE I, BINDING SITE II
and BINDING SITE III respectively. It is appreciated that the
number of host target binding sites shown in Fig. 1 is
meant as an illustration only, and is not meant to be limit-
ing VGAM23 RNA, herein designated VGAM RNA, may
have a different number of host target binding sites in
untranslated regions of a VGAM23 host target RNA, herein
designated VGAM HOST TARGET RNA. It is further appre-
ciated that while Fig. 1 depicts host target binding sites in
the 3UTR region, this is meant as an example only these
host target binding sites may be located in the 3UTR re-
gion, the 5UTR region, or in both 3UTR and 5UTR regions.

[0282]   The complementary binding of VGAM23 RNA, herein des-

ignated VGAM RNA, to host target binding sites on VGAM23 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM23 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM23 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0283] It is appreciated that VGAM23 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM23 host target genes. The mRNA of each one of this plurality of VGAM23 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM23 RNA, herein designated VGAM RNA, and which when bound by VGAM23 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM23 host target proteins.

[0284] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM23 gene, herein designated VGAM GENE, on one or more VGAM23 host target gene, herein designated VGAM

HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0285] It is yet further appreciated that a function of VGAM23 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM23 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM23 correlate with, and may be deduced from, the identity of the host target genes which VGAM23 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0286] Nucleotide sequences of the VGAM23 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

diced VGAM23 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM23 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM23 are further described hereinbelow with reference to Table 1.

[0287] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM23 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0288] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 24 (VGAM24) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0289] VGAM24 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM24 was detected is described hereinabove with reference to Figs. 2-8.

[0290] VGAM24 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodefi-

ciency virus 1. VGAM24 host target gene, herein desig-
nated VGAM HOST TARGET GENE, is a human gene con-
tained in the human genome.

[0291] VGAM24 gene, herein designated VGAM GENE, encodes a
VGAM24 precursor RNA, herein designated VGAM PRE-
CURSOR RNA. Similar to other miRNA genes, and unlike
most ordinary genes, VGAM24 precursor RNA, herein des-
ignated VGAM PRECURSOR RNA, does not encode a pro-
tein. A nucleotide sequence identical or highly similar to
the nucleotide sequence of VGAM24 precursor RNA is
designated SEQ ID:10, and is provided hereinbelow with
reference to the sequence listing part. Nucleotide se-
quence SEQ ID:10 is located at position 1301 relative to
the genome of Human immunodeficiency virus 1.

[0292] VGAM24 precursor RNA, herein designated VGAM PRE-
CURSOR RNA, folds onto itself, forming VGAM24 folded
precursor RNA, herein designated VGAM FOLDED PRECUR-
SOR RNA, which has a two-dimensional hairpin structure.
As is well known in the art, this hairpin structure, is typi-
cal of RNA encoded by miRNA genes, and is due to the
fact that the nucleotide sequence of the first half of the
RNA encoded by a miRNA gene is an accurate or partial
inversed-reversed sequence of the nucleotide sequence of

the second half thereof.

[0293] An enzyme complex designated DICER COMPLEX, dices the VGAM24 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM24 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 8700%) nucleotide sequence of VGAM24 RNA is designated SEQ ID:25, and is provided hereinbelow with reference to the sequence listing part.

[0294] VGAM24 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM24 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM24 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0295] VGAM24 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM24 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM24 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM24 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM24 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0296] The complementary binding of VGAM24 RNA, herein designated VGAM RNA, to host target binding sites on VGAM24 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM24 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM24 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0297] It is appreciated that VGAM24 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM24 host target genes. The mRNA of each one of this plurality of VGAM24 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM24 RNA, herein designated VGAM RNA, and which when bound by VGAM24 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM24 host target proteins.

[0298] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM24 gene, herein designated VGAM GENE, on one or more VGAM24 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with

reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0299] It is yet further appreciated that a function of VGAM24 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM24 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM24 correlate with, and may be deduced from, the identity of the host target genes which VGAM24 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0300] Nucleotide sequences of the VGAM24 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM24 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of

VGAM24 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM24 are further described hereinbelow with reference to Table 1.

[0301] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM24 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0302] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 25 (VGAM25) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0303] VGAM25 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM25 was detected is described hereinabove with reference to Figs. 2-8.

[0304] VGAM25 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM25 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene con-

tained in the human genome.

[0305] VGAM25 gene, herein designated VGAM GENE, encodes a VGAM25 precursor RNA, herein designated VGAM PRE-CURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM25 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM25 precursor RNA is designated SEQ ID:11, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:11 is located at position 9080 relative to the genome of Human immunodeficiency virus 1.

[0306] VGAM25 precursor RNA, herein designated VGAM PRE-CURSOR RNA, folds onto itself, forming VGAM25 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0307] An enzyme complex designated DICER COMPLEX, dices

the VGAM25 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM25 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 9000%) nucleotide sequence of VGAM25 RNA is designated SEQ ID:26, and is provided hereinbelow with reference to the sequence list-ing part.

[0308] VGAM25 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM25 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM25 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untrans-lated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR re-spectively.

[0309] VGAM25 RNA, herein designated VGAM RNA, binds com-plementarily to one or more host target binding sites lo-cated in untranslated regions of VGAM25 host target RNA,

herein designated VGAM HOST TARGET RNA. This com-plementary binding is due to the fact that the nucleotide sequence of VGAM25 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-ing VGAM25 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM25 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appre-ciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR re-gion, the 5UTR region, or in both 3UTR and 5UTR regions.

[0310] The complementary binding of VGAM25 RNA, herein des-ignated VGAM RNA, to host target binding sites on VGAM25 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM25 host tar-

get RNA, herein designated VGAM HOST TARGET RNA, into VGAM25 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0311] It is appreciated that VGAM25 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM25 host target genes. The mRNA of each one of this plurality of VGAM25 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-plementary to VGAM25 RNA, herein designated VGAM RNA, and which when bound by VGAM25 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM25 host target proteins.

[0312] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM25 gene, herein designated VGAM GENE, on one or more VGAM25 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only

for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0313] It is yet further appreciated that a function of VGAM25 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM25 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM25 correlate with, and may be deduced from, the identity of the host target genes which VGAM25 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0314] Nucleotide sequences of the VGAM25 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM25 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM25 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM25 are further de-

scribed hereinbelow with reference to Table 1.

[0315] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM25 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0316] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 26 (VGAM26) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0317] VGAM26 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM26 was detected is described hereinabove with reference to Figs. 2-8.

[0318] VGAM26 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM26 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0319] VGAM26 gene, herein designated VGAM GENE, encodes a

VGAM26 precursor RNA, herein designated VGAM PRE-CURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM26 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM26 precursor RNA is designated SEQ ID:12, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:12 is located at position 2049 relative to the genome of Human immunodeficiency virus 1.

[0320] VGAM26 precursor RNA, herein designated VGAM PRE-CURSOR RNA, folds onto itself, forming VGAM26 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0321] An enzyme complex designated DICER COMPLEX, dices the VGAM26 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM26 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 7200%) nucleotide sequence of VGAM26 RNA is designated SEQ ID:27, and is provided hereinbelow with reference to the sequence list- ing part.

[0322] VGAM26 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM26 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM26 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untrans- lated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR re- spectively.

[0323] VGAM26 RNA, herein designated VGAM RNA, binds com- plementarily to one or more host target binding sites lo- cated in untranslated regions of VGAM26 host target RNA, herein designated VGAM HOST TARGET RNA. This com- plementary binding is due to the fact that the nucleotide

sequence of VGAM26 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM26 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM26 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0324] The complementary binding of VGAM26 RNA, herein designated VGAM RNA, to host target binding sites on VGAM26 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM26 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM26 host target protein, herein designated VGAM

HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0325] It is appreciated that VGAM26 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM26 host target genes. The mRNA of each one of this plurality of VGAM26 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-plementary to VGAM26 RNA, herein designated VGAM RNA, and which when bound by VGAM26 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM26 host target proteins.

[0326] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM26 gene, herein designated VGAM GENE, on one or more VGAM26 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also

believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0327] It is yet further appreciated that a function of VGAM26 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM26 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM26 correlate with, and may be deduced from, the identity of the host target genes which VGAM26 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0328] Nucleotide sequences of the VGAM26 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM26 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM26 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM26 are further described hereinbelow with reference to Table 1.

[0329] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM26 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0330] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 27 (VGAM27) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0331] VGAM27 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM27 was detected is described hereinabove with reference to Figs. 2-8.

[0332] VGAM27 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM27 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0333] VGAM27 gene, herein designated VGAM GENE, encodes a VGAM27 precursor RNA, herein designated VGAM PRE-CURSOR RNA. Similar to other miRNA genes, and unlike

most ordinary genes, VGAM27 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM27 precursor RNA is designated SEQ ID:13, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:13 is located at position 1810 relative to the genome of Human immunodeficiency virus 1.

[0334] VGAM27 precursor RNA, herein designated VGAM PRECURSOR RNA, folds onto itself, forming VGAM27 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0335] An enzyme complex designated DICER COMPLEX, dices the VGAM27 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM27 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 6000%) nucleotide sequence of VGAM27 RNA is designated SEQ ID:28, and is provided hereinbelow with reference to the sequence listing part.

[0336] VGAM27 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM27 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM27 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0337] VGAM27 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM27 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM27 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of

the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM27 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM27 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0338] The complementary binding of VGAM27 RNA, herein designated VGAM RNA, to host target binding sites on VGAM27 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM27 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM27 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0339] It is appreciated that VGAM27 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM27 host target genes. The mRNA of each one of this plurality of VGAM27 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-plementary to VGAM27 RNA, herein designated VGAM RNA, and which when bound by VGAM27 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM27 host target proteins.

[0340] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM27 gene, herein designated VGAM GENE, on one or more VGAM27 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although spe-

cific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0341] It is yet further appreciated that a function of VGAM27 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM27 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM27 correlate with, and may be deduced from, the identity of the host target genes which VGAM27 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0342] Nucleotide sequences of the VGAM27 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM27 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM27 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM27 are further described hereinbelow with reference to Table 1.

[0343] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the

complementarity of each of these host target binding sites to VGAM27 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0344] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 28 (VGAM28) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0345] VGAM28 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM28 was detected is described hereinabove with reference to Figs. 2-8.

[0346] VGAM28 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM28 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0347] VGAM28 gene, herein designated VGAM GENE, encodes a VGAM28 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM28 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a pro-

tein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM28 precursor RNA is designated SEQ ID:14, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:14 is located at position 728 relative to the genome of Human immunodeficiency virus 1.

[0348] VGAM28 precursor RNA, herein designated VGAM PRE-CURSOR RNA, folds onto itself, forming VGAM28 folded precursor RNA, herein designated VGAM FOLDED PRECUR-SOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0349] An enzyme complex designated DICER COMPLEX, dices the VGAM28 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM28 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 7600%) nucleotide sequence of VGAM28 RNA is designated SEQ ID:29, and is provided hereinbelow with reference to the sequence listing part.

[0350] VGAM28 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM28 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM28 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0351] VGAM28 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM28 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM28 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target

binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM28 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM28 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0352] The complementary binding of VGAM28 RNA, herein designated VGAM RNA, to host target binding sites on VGAM28 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM28 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM28 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0353] It is appreciated that VGAM28 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM28 host target genes. The mRNA of each one of this plurality of VGAM28 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM28 RNA, herein designated VGAM RNA, and which when bound by VGAM28 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM28 host target proteins.

[0354] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM28 gene, herein designated VGAM GENE, on one or more VGAM28 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective:

Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0355] It is yet further appreciated that a function of VGAM28 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM28 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM28 correlate with, and may be deduced from, the identity of the host target genes which VGAM28 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0356] Nucleotide sequences of the VGAM28 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM28 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM28 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM28 are further described hereinbelow with reference to Table 1.

[0357] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM28 RNA, herein designated VGAM RNA, are de-

scribed hereinbelow with reference to Table 2.

[0358] Fig. 1 further provides a conceptual description of another novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 29 (VGAM29) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[0359] VGAM29 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM29 was detected is described hereinabove with reference to Figs. 2-8.

[0360] VGAM29 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human immunodeficiency virus 1. VGAM29 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[0361] VGAM29 gene, herein designated VGAM GENE, encodes a VGAM29 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM29 precursor RNA, herein designated VGAM PRECURSOR RNA, does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM29 precursor RNA is

designated SEQ ID:15, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:15 is located at position 5471 relative to the genome of Human immunodeficiency virus 1.

[0362] VGAM29 precursor RNA, herein designated VGAM PRE-CURSOR RNA, folds onto itself, forming VGAM29 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional hairpin structure. As is well known in the art, this hairpin structure, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[0363] An enzyme complex designated DICER COMPLEX, dices the VGAM29 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, into VGAM29 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, dicing of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 7000%) nucleotide

sequence of VGAM29 RNA is designated SEQ ID:30, and is provided hereinbelow with reference to the sequence listing part.

[0364] VGAM29 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM29 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM29 host target RNA, herein designated VGAM HOST TARGET RNA, comprises three regions, as is typical of mRNA of a protein coding gene: a 5 untranslated region, a protein coding region and a 3 untranslated region, designated 5UTR, PROTEIN CODING and 3UTR respectively.

[0365] VGAM29 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM29 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM29 RNA, herein designated VGAM RNA, is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows 3 such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting VGAM29 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM29 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3UTR region, this is meant as an example only these host target binding sites may be located in the 3UTR region, the 5UTR region, or in both 3UTR and 5UTR regions.

[0366] The complementary binding of VGAM29 RNA, herein designated VGAM RNA, to host target binding sites on VGAM29 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM29 host target RNA, herein designated VGAM HOST TARGET RNA, into VGAM29 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[0367] It is appreciated that VGAM29 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM29 host target genes. The mRNA of each one of this plurality of VGAM29 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM29 RNA, herein designated VGAM RNA, and which when bound by VGAM29 RNA, herein designated VGAM RNA, causes inhibition of translation of respective one or more VGAM29 host target proteins.

[0368] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM29 gene, herein designated VGAM GENE, on one or more VGAM29 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., Perspective: Glimpses of a tiny RNA world, Science 294,779 (2001)).

[0369] It is yet further appreciated that a function of VGAM29 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM29 include diagnosis, prevention and treatment of viral infection by Human immunodeficiency virus 1. Specific functions, and accordingly utilities, of VGAM29 correlate with, and may be deduced from, the identity of the host target genes which VGAM29 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[0370] Nucleotide sequences of the VGAM29 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the diced VGAM29 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM29 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM29 are further described hereinbelow with reference to Table 1.

[0371] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on, and schematic representation of the complementarity of each of these host target binding sites to VGAM29 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[0372] Fig. 9 further provides a conceptual description of novel

bioinformatically detected regulatory viral gene, referred to here as Viral Genomic Record 30(VGR30) viral gene, which encodes an operon-like cluster of novel viral micro RNA-like genes, each of which in turn modulates expression of at least one host target gene, the function and utility of which at least one host target gene is known in the art.

[0373] VGR30 gene, herein designated VGR GENE, is a novel bioinformatically detected regulatory, non protein coding, RNA viral gene. The method by which VGR30 gene was detected is described hereinabove with reference to Figs. 6-15.

[0374] VGR30 gene encodes VGR30 precursor RNA, herein designated VGR PRECURSOR RNA, an RNA molecule, typically several hundred nucleotides long.

[0375] VGR30 precursor RNA folds spatially, forming VGR30 folded precursor RNA, herein designated VGR FOLDED PRECURSOR RNA. It is appreciated that VGR30 folded precursor RNA, herein designated VGR FOLDED PRECURSOR RNA, comprises a plurality of what is known in the art as hairpin structures. These hairpin structures are due to the fact that the nucleotide sequence of VGR30 precursor RNA comprises a plurality of segments, the first half of each

such segment having a nucleotide sequence which is at least a partial inversed-reversed sequence of the second half thereof, as is well known in the art.

[0376] VGR30 folded precursor RNA, herein designated VGR FOLDED PRECURSOR RNA, is naturally processed by cellular enzymatic activity into at least 8 separate VGAM precursor RNAs, VGAM15 precursor RNA, VGAM16 precursor RNA, VGAM17 precursor RNA, VGAM18 precursor RNA, VGAM19 precursor RNA, VGAM20 precursor RNA, VGAM21 precursor RNA and VGAM22 precursor RNA, herein schematically represented by VGAM1 PRECURSOR, VGAM2 PRECURSOR, VGAM3 PRECURSOR, VGAM4 PRE-CURSOR, VGAM5 PRECURSOR, VGAM6 PRECURSOR, VGAM7 PRECURSOR and VGAM8 PRECURSOR respectively, each of which VGAM precursor RNAs being a hairpin shaped RNA segment, corresponding to VGAM PRECUR-SOR RNA of Fig. 8.

[0377] The above mentioned VGAM precursor RNAs are diced by DICER COMPLEX of Fig. 8, yielding respective short RNA segments of about 22 nucleotides in length, VGAM15 RNA, VGAM16 RNA, VGAM17 RNA, VGAM18 RNA, VGAM19 RNA, VGAM20 RNA, VGAM21 RNA and VGAM22 RNA re-spectively, herein schematically represented by VGAM1

RNA, VGAM2 RNA, VGAM3 RNA, VGAM4 RNA, VGAM5 RNA, VGAM6 RNA, VGAM7 RNA and VGAM8 RNA respectively, each of which VGAM RNAs corresponding to VGAM RNA of Fig. 8.

[0378] VGAM15 RNA, herein schematically represented by VGAM1 binds complimentarily to a host target binding site located in an untranslated region of VGAM15 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM15 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA into VGAM15 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN, both of Fig. 1.

[0379] VGAM16 RNA, herein schematically represented by VGAM2 binds complimentarily to a host target binding site located in an untranslated region of VGAM16 host target RNA, herein schematically represented by VGAM2 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby in-

hibiting translation of VGAM16 host target RNA, herein schematically represented by VGAM2 HOST TARGET RNA into VGAM16 host target protein, herein schematically represented by VGAM2 HOST TARGET PROTEIN, both of Fig. 1.

[0380] VGAM17 RNA, herein schematically represented by VGAM3 binds complimentarily to a host target binding site located in an untranslated region of VGAM17 host target RNA, herein schematically represented by VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM17 host target RNA, herein schematically represented by VGAM3 HOST TARGET RNA into VGAM17 host target protein, herein schematically represented by VGAM3 HOST TARGET PROTEIN, both of Fig. 1.

[0381] VGAM18 RNA, herein schematically represented by VGAM4 binds complimentarily to a host target binding site located in an untranslated region of VGAM18 host target RNA, herein schematically represented by VGAM4 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE

I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM18 host target RNA, herein schematically represented by VGAM4 HOST TARGET RNA into VGAM18 host target protein, herein schematically represented by VGAM4 HOST TARGET PROTEIN, both of Fig. 1.

[0382] VGAM19 RNA, herein schematically represented by VGAM5 binds complimentarily to a host target binding site located in an untranslated region of VGAM19 host target RNA, herein schematically represented by VGAM5 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM19 host target RNA, herein schematically represented by VGAM5 HOST TARGET RNA into VGAM19 host target protein, herein schematically represented by VGAM5 HOST TARGET PROTEIN, both of Fig. 1.

[0383] VGAM20 RNA, herein schematically represented by VGAM6 binds complimentarily to a host target binding site located in an untranslated region of VGAM20 host target RNA, herein schematically represented by VGAM6 HOST TARGET RNA, which host target binding site corre-

sponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM20 host target RNA, herein schematically represented by VGAM6 HOST TARGET RNA into VGAM20 host target protein, herein schematically represented by VGAM6 HOST TARGET PROTEIN, both of Fig. 1.

[0384] VGAM21 RNA, herein schematically represented by VGAM7 binds complimentarily to a host target binding site located in an untranslated region of VGAM21 host target RNA, herein schematically represented by VGAM7 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM21 host target RNA, herein schematically represented by VGAM7 HOST TARGET RNA into VGAM21 host target protein, herein schematically represented by VGAM7 HOST TARGET PROTEIN, both of Fig. 1.

[0385] VGAM22 RNA, herein schematically represented by VGAM8 binds complimentarily to a host target binding site located in an untranslated region of VGAM22 host target RNA, herein schematically represented by VGAM8

HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM22 host target RNA, herein schematically represented by VGAM8 HOST TARGET RNA into VGAM22 host target protein, herein schematically represented by VGAM8 HOST TARGET PROTEIN, both of Fig. 1.

[0386] It is appreciated that a function of VGR30 gene, herein designated VGR GENE, is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGR30 gene include diagnosis, prevention and treatment of viral infection by . Specific functions, and accordingly utilities, of VGR30 gene, herein designated VGR GENE, correlate with, and may be deduced from, the identity of the host target genes, which are inhibited by VGAM RNAs comprised in the operon-like cluster of VGR30 gene: VGAM15 host target protein, VGAM16 host target protein, VGAM17 host target protein, VGAM18 host target protein, VGAM19 host target protein, VGAM20 host target protein, VGAM21 host target protein and VGAM22 host target protein, herein schematically represented by VGAM1 HOST TARGET PRO-

TEIN through VGAM HOST TARGET PROTEIN respectively. The function of these host target genes is elaborated hereinabove with reference to VGAM15, VGAM16, VGAM17, VGAM18, VGAM19, VGAM20, VGAM21 and VGAM22

[0387]   Fig. 9 further provides a conceptual description of novel bioinformatically detected regulatory viral gene, referred to here as Viral Genomic Record 31(VGR31) viral gene, which encodes an operon-like cluster of novel viral micro RNA-like genes, each of which in turn modulates expression of at least one host target gene, the function and utility of which at least one host target gene is known in the art.

[0388]   VGR31 gene, herein designated VGR GENE, is a novel bioinformatically detected regulatory, non protein coding, RNA viral gene. The method by which VGR31 gene was detected is described hereinabove with reference to Figs. 6-15.

[0389]   VGR31 gene encodes VGR31 precursor RNA, herein designated VGR PRECURSOR RNA, an RNA molecule, typically several hundred nucleotides long.

[0390]   VGR31 precursor RNA folds spatially, forming VGR31 folded precursor RNA, herein designated VGR FOLDED

PRECURSOR RNA. It is appreciated that VGR31 folded precursor RNA, herein designated VGR FOLDED PRECURSOR RNA, comprises a plurality of what is known in the art as hairpin structures. These hairpin structures are due to the fact that the nucleotide sequence of VGR31 precursor RNA comprises a plurality of segments, the first half of each such segment having a nucleotide sequence which is at least a partial inversed-reversed sequence of the second half thereof, as is well known in the art.

[0391] VGR31 folded precursor RNA, herein designated VGR FOLDED PRECURSOR RNA, is naturally processed by cellular enzymatic activity into at least 7 separate VGAM precursor RNAs, VGAM23 precursor RNA, VGAM24 precursor RNA, VGAM25 precursor RNA, VGAM26 precursor RNA, VGAM27 precursor RNA, VGAM28 precursor RNA and VGAM29 precursor RNA, herein schematically represented by VGAM1 PRECURSOR, VGAM2 PRECURSOR, VGAM3 PRECURSOR, VGAM4 PRECURSOR, VGAM5 PRECURSOR, VGAM6 PRECURSOR and VGAM7 PRECURSOR respectively, each of which VGAM precursor RNAs being a hairpin shaped RNA segment, corresponding to VGAM PRECURSOR RNA of Fig. 8.

[0392] The above mentioned VGAM precursor RNAs are diced by

DICER COMPLEX of Fig. 8, yielding respective short RNA segments of about 22 nucleotides in length, VGAM23 RNA, VGAM24 RNA, VGAM25 RNA, VGAM26 RNA, VGAM27 RNA, VGAM28 RNA and VGAM29 RNA respectively, herein schematically represented by VGAM1 RNA, VGAM2 RNA, VGAM3 RNA, VGAM4 RNA, VGAM5 RNA, VGAM6 RNA and VGAM7 RNA respectively, each of which VGAM RNAs corresponding to VGAM RNA of Fig. 8.

[0393] VGAM23 RNA, herein schematically represented by VGAM1 binds complimentarily to a host target binding site located in an untranslated region of VGAM23 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM23 host target RNA, herein schematically represented by VGAM1 HOST TARGET RNA into VGAM23 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN, both of Fig. 1.

[0394] VGAM24 RNA, herein schematically represented by VGAM2 binds complimentarily to a host target binding site located in an untranslated region of VGAM24 host

target RNA, herein schematically represented by VGAM2 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM24 host target RNA, herein schematically represented by VGAM2 HOST TARGET RNA into VGAM24 host target protein, herein schematically represented by VGAM2 HOST TARGET PROTEIN, both of Fig. 1.

[0395] VGAM25 RNA, herein schematically represented by VGAM3 binds complimentarily to a host target binding site located in an untranslated region of VGAM25 host target RNA, herein schematically represented by VGAM3 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM25 host target RNA, herein schematically represented by VGAM3 HOST TARGET RNA into VGAM25 host target protein, herein schematically represented by VGAM3 HOST TARGET PROTEIN, both of Fig. 1.

[0396] VGAM26 RNA, herein schematically represented by VGAM4 binds complimentarily to a host target binding

site located in an untranslated region of VGAM26 host target RNA, herein schematically represented by VGAM4 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM26 host target RNA, herein schematically represented by VGAM4 HOST TARGET RNA into VGAM26 host target protein, herein schematically represented by VGAM4 HOST TARGET PROTEIN, both of Fig. 1.

[0397] VGAM27 RNA, herein schematically represented by VGAM5 binds complimentarily to a host target binding site located in an untranslated region of VGAM27 host target RNA, herein schematically represented by VGAM5 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM27 host target RNA, herein schematically represented by VGAM5 HOST TARGET RNA into VGAM27 host target protein, herein schematically represented by VGAM5 HOST TARGET PROTEIN, both of Fig. 1.

[0398] VGAM28 RNA, herein schematically represented by

VGAM6 binds complimentarily to a host target binding site located in an untranslated region of VGAM28 host target RNA, herein schematically represented by VGAM6 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM28 host target RNA, herein schematically represented by VGAM6 HOST TARGET RNA into VGAM28 host target protein, herein schematically represented by VGAM6 HOST TARGET PROTEIN, both of Fig. 1.

[0399] VGAM29 RNA, herein schematically represented by VGAM7 binds complimentarily to a host target binding site located in an untranslated region of VGAM29 host target RNA, herein schematically represented by VGAM7 HOST TARGET RNA, which host target binding site corresponds to a host target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 1, thereby inhibiting translation of VGAM29 host target RNA, herein schematically represented by VGAM7 HOST TARGET RNA into VGAM29 host target protein, herein schematically represented by VGAM7 HOST TARGET PROTEIN, both of Fig. 1.

[0400]   It is appreciated that a function of VGR31 gene, herein designated VGR GENE, is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGR31 gene include diagnosis, prevention and treatment of viral infection by . Specific functions, and accordingly utilities, of VGR31 gene, herein designated VGR GENE, correlate with, and may be deduced from, the identity of the host target genes, which are inhibited by VGAM RNAs comprised in the operon-like cluster of VGR31 gene: VGAM23 host target protein, VGAM24 host target protein, VGAM25 host target protein, VGAM26 host target protein, VGAM27 host target protein, VGAM28 host target protein and VGAM29 host target protein, herein schematically represented by VGAM1 HOST TARGET PROTEIN through VGAM HOST TARGET PROTEIN respectively. The function of these host target genes is elaborated hereinabove with reference to VGAM23, VGAM24, VGAM25, VGAM26, VGAM27, VGAM28 and VGAM29

[0401]   BIBLIOGRAPHY

[0402]   It is appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather the scope

of the present invention includes both combinations and subcombinations of the various features described hereinabove as well as variations and modifications which would occur to persons skilled in the art upon reading the specifications and which are not in the prior art.

[0403] 1.Simard, J.; Berube, D.; Sandberg, M.; Grzeschik, K.-H.; Gagne,R.; Hansson, V.; Jahnsen, T.: Assignment of the gene encoding thecatalytic subunit C-beta of cAMP-dependent protein kinase to the p36band on chromosome 1. Hum. Genet. 88: 653-657, 1992.

[0404] 2.Elliott, K. J.; Ellis, S. B.; Berckhan, K. J.; Urrutia, A.; Chavez-Noriega,L. E.; Johnson, E. C.; Velicelebi, G.; Harpold, M. M.: Comparativestructure of human neuronal alpha(2)-alpha(7) and beta(2)-beta(4)nicotinic acetylcholine receptor subunits and functional expressionof the alpha(2), alpha(3), alpha(4), alpha(7), beta(2), and beta(4)subunits. J. Molec. Neurosci. 7: 217-228, 1996.

[0405] 3.Seldin, M. F.: Personal Communication. Durham, N. C. 3/13/1989.

[0406] 4.Mattei, M.-G.; Pebusque, M.-J.; Birnbaum, D.: Chromosomal localizationsof mouse Fgf2 and Fgf5 genes. Mammalian Genome 2: 135-137, 1992.

[0407] 5.Avraham, K. B.; Givol, D.; Avivi, A.; Yayon, A.; Copeland,

N. G.;Jenkins, N. A.: Mapping of murine fibroblast growth factor receptorsrefines regions of homology between mouse and human chromosomes. Genomics 21:656–658, 1994.

[0408]   6.Keegan, K.; Johnson, D. E.; Williams, L. T.; Hayman, M. J.: Isolationof an additional member of the fibroblast growth factor receptor family,FGFR-3. Proc. Nat. Acad. Sci. 88: 1095–1099, 1991.

[0409]   7.Mannick, J. B.; Hausladen, A.; Liu, L.; Hess, D. T.; Zeng, M.;Miao, Q. X.; Kane, L. S.; Gow, A. J.; Stamler, J. S.: Fas-inducedcaspase denitrosylation. Science 284: 651–654, 1999.

[0410]   8.Groot Kormelink, P. J.; Luyten, W. H. M. L.: Cloning and sequenceof full-length cDNAs encoding the human neuronal nicotinic acetylcholinereceptor (nAChR) subunits beta-3 and beta-4 and expression of sevennAChR subunits in the human neuroblastoma cell line SH-SY5Y and/orIMR-32. FEBS Lett. 400: 309–314, 1997.

[0411]   9.Bauer, H.; Mayer, H.; Marchler-Bauer, A.; Salzer, U.; Prohaska,R.: Characterization of p40/GPR69A as a peripheral membrane proteinrelated to the lantibiotic synthetase component C. Biochem. Biophys.Res. Commun. 275: 69–74, 2000.

[0412] 10.Mayer, H.; Bauer, H.; Prohaska, R.: Organization and chromosomallocalization of the human and mouse genes coding for LanC-like protein1 (LANCL1). Cytogenet. Cell Genet. 93: 100-104, 2001.

[0413] 11.Mayer, H.; Salzer, U.; Breuss, J.; Ziegler, S.; Marchler-Bauer,A.; Prohaska, R.: Isolation, molecular characteriza-tion, and tissue-specificexpression of a novel putative G protein-coupled receptor. Biochim.Biophys. Acta 1395: 301-308, 1998.

[0414] 12.Li, S.-H.; Lam, S.; Cheng, A. L.; Li, X.-J.: Intranuclear huntingtinincreases the expression of caspase-1 and in-duces apoptosis. Hum.Molec. Genet. 9: 2859-2867, 2000.

[0415] 13.Duke-Cohan, J. S.; Gu, J.; McLaughlin, D. F.; Xu, Y.; Freeman,G. J.; Schlossman, S. F.: Attractin (DPPT-L), a member of the CUBfamily of cell adhesion and guidance proteins, is secreted by activatedhuman T lymphocytes and modulates immune cell interactions. Proc.Nat. Acad. Sci. 95: 11336-11341, 1998.

[0416] 14.Gunn, T. M.; Miller, K. A.; He, L.; Hyman, R. W.; Davis, R. W.;Azarani, A.; Schlessman, S. F.; Duke-Cohan, J. S.; Barsh, G. S.:The mouse mahogany locus encodes a trans-membrane form of human attractin. Nature 398:152-156, 1999.

[0417] 15.He, L.; Gunn, T. M.; Bouley, D. M.; Lu, X.-Y.; Watson, S. J.; Schlossman,S. F.; Duke-Cohan, J. S.; Barsh, G. S.: A biochemical function forattractin in agouti-induced pigmentation and obesity. Nature Genet. 27:40-47, 2001.

[0418] 16.Tang, W.; Gunn, T. M.; McLaughlin, D. F.; Barsh, G. S.; Schlossman,S. F.; Duke-Cohan, J. S.: Secreted and membrane attractin resultfrom alternative splicing of the human ATRN gene. Proc. Nat. Acad.Sci. 97: 6025-6030, 2000.

[0419] 17.Dionne, C. A.; Kaplan, R.; Seuanez, H.; O'Brien, S. J.; Jaye, M.: Chromosome assignment by polymerase chain reaction techniques: assignmentof the oncogene FGF-5 to human chromosome 4. Biotechniques 8: 190-194,1990.

[0420] 18.Hebert, J. M.; Rosenquist, T.; Gotz, J.; Martin, G. R.: FGF5 asa regulator of the hair growth cycle: evidence from targeted and spontaneousmutations. Cell 78: 1017-1025, 1994.

[0421] 19.Nguyen, C.; Roux, D.; Mattei, M.-G.; de Lapeyriere, O.; Goldfarb,M.; Birnbaum, D.; Jordan, B. R.: The FGF-related oncogenes hst andint.2, and the bcl.1 locus are contained within one megabase in bandq13 of chromosome 11, while the fgf.5 oncogene maps to 4q21. Oncogene 3:703-708, 1988.

[0422] 20.Zhan, X.; Bates, B.; Hu, X.; Goldfarb, M.: The human FGF-5 oncogeneencodes a novel protein related to fibroblast growth factors. Molec.Cell. Biol. 8: 3487-3495, 1988.

[0423] 21.Douhan, J., III; Hauber, I.; Eibl, M. M.; Glimcher, L. H.: Geneticevidence for a new type of major histocompatibility complex classII combined immunodeficiency characterized by a dyscoordinate regulationof HLA-D alpha and beta chains. J. Exp. Med. 183: 1063-1069, 1996.

[0424] 22.Pan, H.; Yin, C.; Dyson, N. J.; Harlow, E.; Yamasaki, L.; VanDyke, T.: Key roles for E2F1 in signaling p53-dependent apoptosisand in cell division within developing tumors. Molec. Cell 2: 283-292,1998.

[0425] 23.Phillips, A. C.; Ernst, M. K.; Bates, S.; Rice, N. R.; Vousden,K. H.: E2F-1 potentiates cell death by blocking anti-apoptotic signalingpathways. Molec. Cell 4: 771-781, 1999.

[0426] 24.Saenz Robles, M. T.; Symonds, H.; Chen, J.; Van Dyke, T.: Inductionversus progression of brain tumor development: differential functionsfor the pRB- and p53-targeting domains of simian virus 40 T antigen. Molec.Cell. Biol. 14: 2686-2698, 1994.

[0427] 25.Sherr, C. J.: Tumor surveillance via the ARF-p53 pathway. GenesDev. 12: 2984-2991, 1998.

[0428] 26.Tsai, K. Y.; Hu, Y.; Macleod, K. F.; Crowley, D.; Ya-
masaki, L.;Jacks, T.: Mutation of E2f-1 suppresses apop-
tosis and inappropriateS phase entry and extends survival
of Rb-deficient mouse embryos. Molec.Cell 2: 293-304,
1998.

[0429] 27.Weinberg, R. A.: E2F and cell proliferation: a world
turned upsidedown. Cell 85: 457-459, 1996.

[0430] 28.Wu, L.; Timmers, C.; Maiti, B.; Saavedra, H. I.; Sang, L.;
Chong,G. T.; Nuckolls, F.; Giangrande, P.; Wright, F. A.;
Field, S. J.;Greenberg, M. E.; Orkin, S.; Nevins, J. R.; Robin-
son, M. L.; Leone,G.: The E2F1-3 transcription factors are
essential for cellular proliferation. Nature 414:457-462,
2001.

[0431] 29.Yamasaki, L.; Jacks, T.; Bronson, R.; Goillot, E.; Harlow,
E.;Dyson, N. J.: Tumor induction and tissue atrophy in
mice lackingE2F-1. Cell 85: 537-548, 1996.

[0432] 30.Zhang, H. S.; Postigo, A. A.; Dean, D. C.: Active tran-
scriptionalrepression by the Rb-E2F complex mediates G1
arrest triggered by p16(INK4a),TGF-beta, and contact in-
hibition. Cell 97: 53-61, 1999.

[0433] 31.Zhang, Y.; Chellappan, S. P.: Cloning and characteriza-
tion ofhuman DP2, a novel dimerization partner of E2F.
Oncogene 10: 2085-2093,1995.

[0434] 32.Nagase, T.; Ishikawa, K.; Nakajima, D.; Ohira, M.; Seki, N.; Miyajima,N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O.: Prediction ofthe coding sequences of unidentified human genes. VII. The completesequences of 100 new cDNA clones from brain which can code for largeproteins in vitro. DNA Res. 4: 141-150, 1997.

[0435] 33.Hu, X.; Ray, P. N.; Murphy, E. G.; Thompson, M. W.; Worton, R.G.: Duplicational mutation at the Duchenne muscular dystrophy locus:its frequency, distribution, origin, and phenotype-genotype correlation. Am.J. Hum. Genet. 46: 682-695, 1990.

[0436] 34.Hu, X.; Ray, P. N.; Worton, R. G.: Mechanisms of tandem duplicationin the Duchenne muscular dystrophy gene include both homologous andnonhomologous intrachromosomal recombination. EMBO J. 10: 2471-2477,1991.

[0437] 35.Hu, X.; Worton, R. G.: Partial gene duplication as a cause ofhuman disease. Hum. Mutat. 1: 3-12, 1992.

[0438] 36.Ingram, V. M.: Gene evolution and the haemoglobins. Nature 189:704-708, 1961.

[0439] 37.Itagaki, Y.; Saida, K.; Iwamura, K.: Regenerative capacity ofmdx mouse muscles after repeated applications of myo-necrotic bupivacaine. ActaNeuropath. 89: 380-384, 1995.

[0440] 38.Kaplan, J.-C.; Kahn, A.; Chelly, J.: Illegitimate transcription:its use in the study of inherited disease. Hum. Mutat. 1: 357-360,1992.

[0441] 39.Kavaslar, G. N.; Telatar, M.; Serdaroglu, P.; Deymeer, F.; Ozdemir,C.; Tolun, A.: Identification of a one-basepair deletion in exon6 of the dystrophin gene. Hum. Mutat. 6: 85-86, 1995.

[0442] 40.Kilimann, M. W.; Pizzuti, A.; Grompe, M.; Caskey, C. T.: Pointmutations and polymorphisms in the human dystrophin gene identifiedin genomic DNA sequences amplified by multiplex PCR. Hum. Genet. 89:253-258, 1992.

[0443] 41.Kim, T.-W.; Wu, K.; Black, I. B.: Deficiency of brain synapticdystrophin in human Duchenne muscular dystrophy. Ann. Neurol. 38:446-449, 1995.

[0444] 42.Kneppers, A. L. J.; Deutz-Terlouw, P. P.; van Ommen, G. J. B.;Bakker, E.: Point mutation screening for Duchenne muscular dystrophy(DMD) by SSCP-analysis of multiplex PCR products by use of the PhastSystem(TM). Am. J. Hum. Genet. Suppl. 53: Abstract-1493, 1993.

[0445] 43.Koenig, M.: Personal Communication. Boston, Mass. 10/8/1987.100. Koenig, M.; Beggs, A. H.; Moyer, M.; Scherpf, S.; Heindrich,K.; Bettecken, T.; Meng, G.; Muller, C. R.; Lindlof, M.; Kaariainen,H.; de la Chapelle, A.; Kiuru,

A.; and 24 others: The molecularbasis for Duchenne versus Becker muscular dystrophy: correlation ofseverity with type of deletion. Am. J. Hum. Genet. 45: 498-506,1989.101. Koenig, M.; Bertelson, C. J.; Monaco, A. P.; Hoffman, E.; Feener,C. C.; Kunkel, L. M.: Complete cloning of the Duchenne muscular dystrophycDNA and an analysis of the entire DMD locus. (Abstract) Am. J. Hum.Genet. 41: A222, 1987.102. Koenig, M.; Hoffman, E. P.; Bertelson, C. J.; Monaco, A. P.;Feener, C.; Kunkel, L. M.: Complete cloning of the Duchenne musculardystrophy (DMD) cDNA and preliminary genomic organization of the DMDgene in normal and affected individuals. Cell 50: 509-517, 1987.103. Koenig, M.; Monaco, A. P.; Kunkel, L. M.: The complete sequenceof dystrophin predicts a rod-shaped cytoskeletal protein. Cell 53:219-228, 1988.104. Koh, J.; Bartlett, R. J.; Pericak-Vance, M. A.; Speer, M. C.;Yamaoka, L. H.; Phillips, K.; Hung, W.-Y.; Ray, P. N.; Worton, R.G.; Gilbert, J. R.; Lee, J. E.; Siddique, T.; Kandt, R. S.; Roses,A. D.: Inherited deletion at Duchenne dystrophy locus in normal male.(Letter) Lancet II: 1154-1155, 1987.105. Kunkel, L. M.: Analysis of deletions in DNA from patients withBecker and Duchenne muscular dystrophy. Nature 322: 73-77, 1986.106. Kunkel, L. M.;

Monaco, A. P.; Middlesworth, W.; Ochs, H. D.;Latt, S. A.:
Specific cloning of DNA fragments absent from the DNAof
a male patient with an X chromosome deletion. Proc. Nat.
Acad.Sci. 82: 4778-4782, 1985.107. Laing, N. G.; Layton,
M. G.; Johnsen, R. D.; Chandler, D. C.;Mears, M. E.; Gold-
blatt, J.; Kakulas, B. A.: Two distinct mutationsin a single
dystrophin gene: chance occurrence or premutation? Am.J.
Med. Genet. 42: 688-692, 1992.108. Lederfein, D.; Levy,
Z.; Augier, N.; Mornet, D.; Morris, G.;Fuchs, O.; Yaffe, D.;
Nudel, U.: A 71-kilodalton protein is a majorproduct of
the Duchenne muscular dystrophy gene in brain and oth-
ernonmuscle tissues. Proc. Nat. Acad. Sci. 89: 5346-5350,
1992.109. Lederfein, D.; Yaffe, D.; Nudel, U.: A house-
keeping type promoter,located in the 3-prime region of
the Duchenne muscular dystrophy gene,controls the ex-
pression of Dp71, a major product of the gene.
Hum.Molec. Genet. 2: 1883-1888, 1993.110. Lee, C. C.;
Pearlman, J. A.; Chamberlain, J. S.; Caskey, C. T.: Expres-
sion of recombinant dystrophin and its localization to the-
cell membrane. Nature 349: 334-336, 1991.111. Lee,
G.-H.; Badorff, C.; Knowlton, K. U.: Dissociation of sarco-
glycansand the dystrophin carboxyl terminus from the
sarcolemma in enteroviralcardiomyopathy. Circ. Res. 87:

489-495, 2000.112. Lenk, U.; Hanke, R.; Kraft, U.; Grade, K.; Grunewald, I.; Speer,A.: Non-isotopic analysis of single strand conformation polymorphism(SSCP) in the exon 13 region of the human dystrophin gene. J. Med.Genet. 30: 951-954, 1993.113. Lenk, U.; Hanke, R.; Speer, A.: Carrier detection in DMD familieswith point mutations, using PCR-SSCP and direct sequencing. Neuromusc.Disord. 4: 411-418, 1994.114. Lenk, U.; Hanke, R.; Thiele, H.; Speer, A.: Point mutationsat the carboxy terminus of the human dystrophin gene: implicationsfor an association with mental retardation in DMD patients. Hum.Molec. Genet. 2: 1877-1881, 1993.115. Lenk, U.; Oexle, K.; Voit, T.; Ancker, U.; Hellner, K.-A.; Speer,A.; Hubner, C.: A cysteine 3340 substitution in the dystroglycan-bindingdomain of dystrophin associated with Duchenne muscular dystrophy,mental retardation and absence of the ERG b-wave. Hum. Molec. Genet. 973-975,1996.116. Liechti-Gallati, S.; Braga, S.; Hirsiger, H.; Moser, H.: Familialdeletion in Becker type muscular dystrophy within the pXJ region. Hum.Genet. 77: 267-268, 1987.117. Lindlof, M.; Kaari-ainen, H.; van Ommen, G. J. B.; de la Chapelle,A.: Microdeletions in patients with X-linked muscular dystrophy:molecular-clinical correlations. Clin. Genet. 33:

131–139, 1988.118. Lindlof, M.; Kiuru, A.; Kaariainen, H.; Kalimo, H.; Lang, H.;Pihko, H.; Rapola, J.; Somer, H.; Somer, M.; Savontaus, M.-L.; dela Chapelle, A.: Gene deletions in X-linked muscular dystrophy. Am.J. Hum. Genet. 44: 496–503, 1989.119. Mankin, A. S.; Liebman, S. W.: Baby, don't stop! Nature Genet. 23:8–10, 1999.120. Mao, Y.; Cremer, M.: Detection of Duchenne muscular dystrophycarriers by dosage analysis using the DMD cDNA clone 8. Hum. Genet. 81:193–195, 1989.121. Matsuo, M.; Masumura, T.; Nakajima, T.; Kitoh, Y.; Takumi, T.;Nishio, H.; Koga, J.; Nakamura, H.: A very small frame-shifting deletionwithin exon 19 of the Duchenne muscular dystrophy gene. Biochem.Biophys. Res. Commun. 170: 963–967, 1990.122. Matsuo, M.; Masumura, T.; Nishio, H.; Nakajima, T.; Kitoh, Y.;Takumi, T.; Koga, J.; Nakamura, H.: Exon skipping during splicingof dystrophin mRNA precursor due to an intraexon deletion in the dystrophingene of Duchenne muscular dystrophy. J. Clin. Invest. 87: 2127–2131,1991.123. McArdle, A.; Edwards, R. H. T.; Jackson, M. J.: Time courseof changes in plasma membrane permeability in the dystrophin-deficientmdx mouse. Muscle Nerve 17: 1378–1384, 1994.124. McCabe, E. R. B.; Towbin, J.; Chamberlain, J.; Baumbach,

L.;Witkowski, J.; van Ommen, G. J. B.; Koenig, M.; Kunkel, L. M.; Seltzer,W. K.: Complementary DNA probes for the Duchenne muscular dystrophylocus demonstrate a previously undetectable deletion in a patientwith dystrophic myopathy, glycerol kinase deficiency, and congenitaladrenal hypoplasia. J. Clin. Invest. 83: 95-99, 1989.125. Milasin, J.; Muntoni, F.; Severini, G. M.; Bartoloni, L.; Vatta,M.; Krajinovic, M.; Mateddu, A.; Angelini, C.; Camerini, F.; Falaschi,A.; Mestroni, L.; Giacca, M.; Heart Muscle Disease Study Group:A point mutation in the 5-prime splice site of the dystrophin genefirst intron responsible for X-linked dilated cardiomyopathy. Hum.Molec. Genet. 5: 73-79, 1996.126. Minetti, C.; Bonilla, E.: Mosaic expression of dystrophin incarriers of Becker's muscular dystrophy and the X-linked syndromeof myalgia and cramps. (Letter) New Eng. J. Med. 327: 1100, 1992.127. Moizard, M.-P.; Toutain, A.; Fournier, D.; Berret, F.; Raynaud,M.; Billard, C.; Andres, C.; Moraine, C.: Severe cognitive impairmentin DMD: obvious clinical indication for Dp71 isoform point mutationscreening. Europ. J. Hum. Genet. 8: 552-556, 2000.128. Monaco, A. P.; Bertelson, C. J.; Liechti-Gallati, S.; Moser,H.; Kunkel, L. M.: An explanation for phenotypic differences betweenpatients

bearing partial deletions of DMD locus. Genomics 2: 90-95,1988.129. Monaco, A. P.; Kunkel, L. M.: A giant locus for the Duchenneand Becker muscular dystrophy gene. Trends Genet. 3: 33-37, 1987.130. Monaco, A. P.; Neve, R. L.; Colletti-Feener, C.; Bertelson, C.J.; Kurnit, D. M.; Kunkel, L. M.: Isolation of candidate cDNAs forportions of the Duchenne muscular dystrophy gene. Nature 323: 646-650,1986.131. Muntoni, F.; Cau, M.; Ganau, A.; Congiu, R.; Arvedi, G.; Mateddu,A.; Marrosu, M. G.; Cianchetti, C.; Realdi, G.; Cao, A.; Melis, M.A.: Deletion of the dystrophin muscle-promoter region associatedwith X-linked dilated cardiomyopathy. New Eng. J. Med. 329: 921-925,1993.132. Muntoni, F.; Melis, M. A.; Ganau, A.; Dubowitz, V.: Transcriptionof the dystrophin gene in normal tissues and in skeletal muscle ofa family with X-linked dilated cardiomyopathy. Am. J. Hum. Genet. 56:151-157, 1995.133. Muntoni, F.; Wilson, L.; Marrosu, G.; Marrosu, M. G.; Cianchetti,C.; Mestroni, L.; Ganau, A.; Dubowitz, V.; Sewry, C.: A mutationin the dystrophin gene selectively affecting dystrophin expressionin the heart. J. Clin. Invest. 96: 693-699, 1995.134. Nevin, N. C.; Hughes, A. E.; Calwell, M.; Lim, J. H. K.: Duchennemuscular dystrophy in a female with a translocation involving

Xp21. J.Med. Genet. 23: 171-187, 1986.135. Nigro, V.;

Politano, L.; Nigro, G.; Romano, S. C.; Molinari,A. M.; Puca,

G. A.: Detection of a nonsense mutation in the dystroph-

ingene by multiple SSCP. Hum. Molec. Genet. 1: 517-520,

1992.136. Nobile, C.; Marchi, J.; Nigro, V.; Roberts, R. G.;

Danieli, G.A.: Exon-intron organization of the human dys-

trophin gene. Genomics 45:421-424, 1997.137. Nobile,

C.; Toffolatti, L.; Rizzi, F.; Simionati, B.; Nigro,V.; Car-

dazzo, B.; Patarnello, T.; Valle, G.; Danieli, G. A.: Analy-

sisof 22 deletion breakpoints in dystrophin intron 49.

Hum. Genet. 110:418-421, 2002.138. Norman, A.;

Harper, P.: A survey of manifesting carriers ofDuchenne

and Becker muscular dystrophy in Wales. Clin. Genet.

36:31-37, 1989.139. Ohno, S.: Evolution by Gene Dupli-

cation. Berlin: Springer-Verlag(pub.) 1970.140. Ortiz-

Lopez, R.; Li, H.; Su, J.; Goytia, V.; Towbin, J. A.:Evidence

for a dystrophin missense mutation as a cause of X-

linkeddilated cardiomyopathy. Circulation 95: 2434-2440,

1997.141. Palmucci, L.; Doriguzzi, C.; Mongini, T.;

Restagno, G.; Chiado-Piat,L.; Maniscalco, M.: Unusual ex-

pression and very mild course of Xp21muscular dystrophy

(Becker type) in a 60-year-old man with 26 percentdele-

tion of the dystrophin gene. Neurology 44: 541-543,

1994.142. Passos-Bueno, M. R.; Bakker, E.; Kneppers, A. L. J.; Takata,R. I.; Rapaport, D.; den Dunnen, J. T.; Zatz, M.; van Ommen, G. J.B.: Different mosaicism frequencies for proximal and distal Duchennemuscular dystrophy (DMD) mutations indicate difference in etiologyand recurrence risk. Am. J. Hum. Genet. 51: 1150-1155, 1992.143. Paulson, K. E.; Deka, N.; Schmid, C. W.; Misra, R.; Schindler,C. W.; Rush, M. G.; Kadyk, L.; Leinwand, L.: A transposon-like elementin human DNA. Nature 316: 359-361, 1985.144. Pernelle, J.-J.; Chafey, P.; Chelly, J.; Wahrmann, J. P.; Kaplan,J.-C.; Tome, F.; Fardeau, M.: Nebulin seen in DMD males includingone patient with a large DNA deletion encompassing the DMD gene. Hum.Genet. 78: 285, 1988.145. Pillers, D.-A. M.; Fitzgerald, K. M.; Duncan, N. M.; Rash, S.M.; White, R. A.; Dwinnell, S. J.; Powell, B. R.; Schnur, R. E.; Ray,P. N.; Cibis, G. W.; Weleber, R. G.: Duchenne/Becker muscular dystrophy:correlation of phenotype by electroretinography with sites of dystrophinmutations. Hum. Genet. 105: 2-9, 1999.146. Pizzuti, A.; Pieretti, M.; Fenwick, R. G.; Gibbs, R. A.; Caskey,C. T.: A transposon-like element in the deletion-prone region ofthe dystrophin gene. Genomics 13: 594-600, 1992.147. Porter, J. D.; Khanna, S.; Kaminski, H. J.; Rao, J. S.; Mer-

riam,A. P.; Richmonds, C. R.; Leahy, P.; Li, J.; Guo, W.; Andrade, F. H.: A chronic inflammatory response dominates the skeletal muscle molecularsignature in dystrophin-deficient mdx mice. Hum. Molec. Genet. 11:263–272, 2002.148. Prior, T. W.; Papp, A. C.; Snyder, P. J.; Burghes, A. H. M.;Bartolo, C.; Sedra, M. S.; Western, L. M.; Mendell, J. R.: A missensemutation in the dystrophin gene in a Duchenne muscular dystrophy patient. NatureGenet. 4: 357–360, 1993.149. Prior, T. W.; Papp, A. C.; Snyder, P. J.; Burghes, A. H. M.;Sedra, M. S.; Western, L. M.; Bartello, C.; Mendell, J. R.: Identificationof two point mutations and a one base deletion in exon 19 of the dystrophingene by heteroduplex formation. Hum. Molec. Genet. 2: 311–313, 1993.150. Prior, T. W.; Papp, A. C.; Snyder, P. J.; Burghes, A. H. M.;Sedra, M. S.; Western, L. M.; Bartolo, C.; Mendell, J. R.: Exon 44nonsense mutation in two-Duchenne muscular dystrophy brothers detectedby heteroduplex analysis. Hum. Mutat. 2: 192–195, 1993.151. Prior, T. W.; Papp, A. C.; Snyder, P. J.; Sedra, M. S.; Western,L. M.; Bartolo, C.; Moxley, R. T.; Mendell, J. R.: Heteroduplex analysisof the dystrophin gene: application to point mutation and carrierdetection. Am. J. Med. Genet. 50: 68–73, 1994.152. Rafael, J. A.; Sunada, Y.; Cole, N. M.; Campbell,

K. P.; Faulkner,J. A.; Chamberlain, J. S.: Prevention of dystrophic pathology inmdx mice by a truncated dystrophin isoform. Hum. Molec. Genet. 3:1725-1733, 1994.153. Rafael, J. A.; Townsend, E. R.; Squire, S. E.; Potter, A. C.;Chamberlain, J. S.; Davies, K. E.: Dystrophin and utrophin influencefiber type composition and post-synaptic membrane structure. Hum.Molec. Genet. 9: 1357-1367, 2000.154. Ray, P. N.; Belfall, B.; Duff, C.; Logan, C.; Kean, V.; Thompson,M. W.; Sylvester, J. E.; Gorski, J. L.; Schmickel, R. D.; Worton,R. G.: Cloning of the breakpoint of an X;21 translocation associatedwith Duchenne muscular dystrophy. Nature 318: 672-675, 1985.155. Read, A. P.; Mountford, R. C.; Forrest, S. M.; Kenwrick, S. J.;Davies, K. E.; Harris, R.: Patterns of exon deletions in Duchenneand Becker muscular dystrophy. Hum. Genet. 80: 152-156, 1988.156. Rininsland, F.; Hahn, A.; Niemann-Seyde, S.; Slomski, R.; Hanefeld,F.; Reiss, J.: Identification of a new DMD gene deletion by ectopictranscript analysis. J. Med. Genet. 29: 647-651, 1992.157. Roberts, R. G.; Bentley, D. R.; Bobrow, M.: Infidelity in thestructure of ectopic transcripts: a novel exon in lymphocyte dystrophintranscripts. Hum. Mutat. 2: 293-299, 1993.158. Roberts, R. G.; Bobrow, M.; Bentley, D. R.: The spectrum

ofmild X-linked recessive muscular dystrophy. Arch. Neurol. 34: 408-416,1992.159. Roberts, R. G.; Bobrow, M.; Bentley, D. R.: Point mutationsin the dystrophin gene. Proc. Nat. Acad. Sci. 89: 2331-2335, 1992.160. Roberts, R. G.; Gardner, R. J.; Bobrow, M.: Searching for the1 in 2,400,000: a review of dystrophin gene point mutations. Hum.Mutat. 4: 1-11, 1994.161. Roberts, R. G.; Passos-Bueno, M. R.; Bobrow, M.; Vainzof, M.;Zatz, M.: Point mutation in a Becker muscular dystrophy patient. Hum.Molec. Genet. 2: 75-77, 1992.162. Rowland, L. P.: Biochemistry of muscle membranes in Duchennemuscular dystrophy. Muscle Nerve 3: 3-20, 1980.163. Ryder-Cook, A. S.; Sicinski, P.; Thomas, K.; Davies, K. E.; Worton,R. G.; Barnard, E. A.; Darlison, M. G.; Barnard, P. J.: Localizationof the mdx mutation within the mouse dystrophin gene. EMBO J. 7:3017-3021, 1988.164. Saad, F. A.; Vita, G.; Mora, M.; Morandi. L.; Vitiello, L.; Oliviero,S.; Danieli, G. A.: A novel nonsense mutation in the human dystrophingene. Hum. Mutat. 2: 314-316, 1993.165. Saad, F. A.; Vita, G.; Toffolatti, L.; Danieli, G. A.: A possiblemissense mutation detected in the dystrophin gene by double strandconformation analysis (DSCA). Neuromusc. Disord. 4: 335-341, 1994.166. Sakamoto, M.; Yuasa, K.;

Yoshimura, M.; Yokota, T.; Ikemoto,T.; Suzuki, M.; Dickson, G.; Miyagoe-Suzuki, Y.; Takeda, S.: Micro-dystrophincDNA ameliorates dystrophic phenotypes when introduced into mdx miceas a transgene. Biochem. Biophys. Res. Commun. 293: 1265-1272, 2002.167. Sarig, R.; Mezger-Lallemand, V.; Gitelman, I.; Davis, C.; Fuchs,O.; Yaffe, D.; Nudel, U.: Targeted inactivation of Dp71, the majornon-muscle product of the DMD gene: differential activity of the Dp71promoter during development. Hum. Molec. Genet. 8: 1-10, 1999.168. Sarkar, G.; Sommer, S. S.: Access to a messenger RNA sequenceor its protein product is not limited by tissue or species specificity. Science 244:331-334, 1989.169. Schwartz, L. S.; Tarleton, J.; Popovich, B.; Seltzer, W. K.;Hoffman, E. P.: Fluorescent multiplex linkage analysis and carrierdetection for Duchenne/Becker muscular dystrophy. Am. J. Hum. Genet. 51:721-729, 1992.170. Scott, M. O.; Sylvester, J. E.; Heiman-Patterson, T.; Shi, Y.-J.;Fieles, W.; Stedman, H.; Burghes, A.; Ray, P.; Worton, R.; Fischbeck,K. H.: Duchenne muscular dystrophy gene expression in normal anddiseased human muscle. Science 239: 1418-1420, 1988.171. Sharp, N. J. H.; Kornegay, J. N.; Van Camp, S. D.; Herbstreith,M. H.; Secore, S. L.; Kettle, S.;

Hung, W.-Y.; Constantinou, C. D.;Dykstra, M. J.; Roses, A. D.; Bartlett, R. J.: An error in dystrophinmRNA processing in golden retriever muscular dystrophy, an animalhomologue of Duchenne muscular dystrophy. Genomics 13: 115-121,1992.172. Shiga, N.; Takeshima, Y.; Sakamoto, H.; Inoue, K.; Yokota, Y.;Yokoyama, M.; Matsuo, M.: Disruption of the splicing enhancer sequencewithin exon 27 of the dystrophin gene by a nonsense mutation inducespartial skipping of the exon and is responsible for Becker musculardystrophy. J. Clin. Invest. 100: 2204-2210, 1997.173. Sicinski, P.; Geng, Y.; Ryder-Cook, A. S.; Barnard, E. A.; Darlison,M. G.; Barnard, P. J.: The molecular basis of muscular dystrophyin the mdx mouse: a point mutation. Science 244: 1578-1580, 1989.174. Smithies, O.; Connell, G. E.; Dixon, G. H.: Chromosomal rearrangementsand the evolution of haptoglobin genes. Nature 196: 232-236, 1962.175. Southern, E. M.: Detection of specific sequences among DNA fragmentsseparated by gel electrophoresis. J. Molec. Biol. 98: 503-517, 1975.176. Stratford-Perricaudet, L. D.; Makeh, I.; Perricaudet, M.; Briand,P.: Widespread long-term gene transfer to mouse skeletal musclesand heart. J. Clin. Invest. 90: 626-630, 1992.177. Takeshima, Y.; Nishio, H.; Narita, N.; Wada, H.;

Ishikawa, Y.;Ishikawa, Y.; Minami, R.; Nakamura, H.; Matsuo, M.: Amino-terminaldeletion of 53% of dystrophin results in an intermediate Duchenne-Beckermuscular dystrophy phenotype. Neurology 44: 1648-1651, 1994.178. Tennyson, C. N.; Klamut, H. J.; Worton, R. G.: The human dystrophingene requires 16 hours to be transcribed and is cotranscriptionallyspliced. Nature Genet. 9: 184-190, 1995.179. Tinsley, J. M.; Blake, D. J.; Davies, K. E.: Apo-dystrophin-3:a 2.2kb transcript from the DMD locus encoding the dystrophin glycoproteinbinding site. Hum. Molec. Genet. 2: 521-524, 1993.180. Tinsley, J. M.; Potter, A. C.; Phelps, S. R.; Fisher, R.; Trickett,J. I.; Davies, K. E.: Amelioration of the dystrophic phenotype ofmdx mice using a truncated utrophin transgene. Nature 384: 349-353,1996.181. Todorova, A.; Danieli, G. A.: Large majority of single-nucleotidemutations along the dystrophin gene can be explained by more thanone mechanism of mutagenesis. Hum. Mutat. 9: 537-547, 1997.182. Torelli, S.; Muntoni, F.: Alternative splicing of dystrophinexon 4 in normal human muscle. Hum. Genet. 97: 521-523, 1996.183. Towbin, J. A.; Hejtmancik, J. F.; Brink, P.; Gelb, B.; Zhu, X.M.; Chamberlain, J. S.; McCabe, E. R. B.; Swift, M.: X-linked dilatedcardiomyopathy: molecular ge-

netic evidence of linkage to the Duchennemuscular dystrophy (dystrophin) gene at the Xp21 locus. Circulation 87:1854–1865, 1993.184. Towbin, J. A.; Ortiz–Lopez, R.: X–linked dilated cardiomyopathy.(Letter) New Eng. J. Med. 330: 369–370, 1994.185. Towbin, J. A.; Zhu, X. M.; Gelb, B.; Bies, R.; Chamberlain, J.;Maichele, A.; Ohlendieck, K.; Campbell, K.; McCabe, E. R. B.; Swift,M.: X–linked dilated cardiomyopathy (XLCM): molecular characterization.(Abstract) Am. J. Hum. Genet. 49 (suppl.): 421, 1991.186. Tuffery, S.; Lenk, U.; Roberts, R. G.; Coubes, C.; Demaille,J.; Claustres, M.: Protein truncation test: analysis of two novelpoint mutations at the carboxy–terminus of the human dystrophin geneassociated with mental retardation. Hum. Mutat. 6: 126–135, 1995.187. Valentine, B. A.; Winand, N. J.; Pradhan, D.; Moise, N. S.; deLahunta, A.; Kornegay, J. N.; Cooper, B. J.: Canine X–linked musculardystrophy as an animal model of Duchenne muscular dystrophy: a review. Am.J. Med. Genet. 42: 352–356, 1992.188. Verellen–Dumoulin, C.; Freund, M.; De Meyer, R.; Laterre, C.;Frederic, J.; Thompson, M. W.; Markovic, V. D.; Worton, R. G.: Expressionof an X–linked muscular dystrophy in a female due to translocationinvolving Xp21 and non–random inactivation of the normal X chromosome.

Hum.Genet. 67: 115-119, 1984.189. Wehling, M.; Spencer, M. J.; Tidball, J. G.: A nitric oxidesynthase transgene ameliorates muscular dystrophy in mdx mice. J.Cell Biol. 155: 123-131, 2001.190. Werner, W.; Spiegler, A. W. J.: Inherited deletion of subbandXp21.13 in a male with Duchenne muscular dystrophy. J. Med. Genet. 25:377-382, 1988.191. Wilton, S. D.; Chandler, D. C.; Kakulas, B. A.; Laing, N. G.: Identification of a point mutation and germinal mosaicism in a Duchennemuscular dystrophy family. Hum. Mutat. 3: 133-140, 1994.192. Wilton, S. D.; Johnsen, R. D.; Pedretti, J. R.; Laing, N. G.: Two distinct mutations in a single dystrophin gene: identificationof an altered splice-site as the primary Becker muscular dystrophymutation. Am. J. Med. Genet. 46: 563-569, 1993.193. Winnard, A. V.; Jia-Hsu, Y.; Gibbs, R. A.; Mendell, J. R.; Burghes,A. H. M.: Identification of a 2 base pair nonsense mutation causinga cryptic splice site in a DMD patient. Hum. Molec. Genet. 1: 645-646,1992.194. Wood, D. S.; Zeviani, M.; Prelle, A.; Bonilla, E.; Salviati,G.; Miranda, A. F.; DiMauro, S.; Rowland, L. P.: Is nebulin the defectivegene product in Duchenne muscular dystrophy? (Letter) New Eng. J.Med. 316: 107-108, 1987.195. Worton, R. G.: Dystrophin: the long and short of it. (Editorial)

J.Clin. Invest. 93: 4, 1994.196. Worton, R. G.: Personal Communication. Toronto, Ontario, Canada 9/12/1987.197. Xiong, D.; Lee, G.-H.; Badorff, C.; Dorner, A.; Lee, S.; Wolf,P.; Knowlton, K. U.: Dystrophin deficiency markedly increases enterovirus-inducedcardiomyopathy: a genetic predisposition to viral heart disease. NatureMed. 8: 872-877, 2002.198. Yang, T. P.; Patel, P. I.; Chinault, A. C.; Stout, J. T.; Jackson,L. G.; Hildebrand, B. M.; Caskey, C. T.: Molecular evidence for newmutation at the HPRT locus in Lesch-Nyhan patients. Nature 310:412-414, 1984.199. Yoshida, K.; Ikeda, S.; Nakamura, A.; Kagoshima, M.; Takeda,S.; Shoji, S.; Yanagisawa, N.: Molecular analysis of the Duchennemuscular dystrophy gene in patients with Becker muscular dystrophypresenting with dilated car-diomyopathy. Muscle Nerve 16: 1161-1166,1993.200. Yoshida, K.; Nakamura, A.; Yazaki, M.; Ikeda, S.; Takeda, S.: Insertional mutation by transposable element, L1, in the DMD generesults in X-linked dilated cardiomyopathy. Hum. Molec. Genet. 7:1129-1132, 1998.201. Zubrzycka-Gaarn, E. E.; Bulman, D. E.; Karpati, G.; Burghes,A. H. M.; Belfall, B.; Klamut, H. J.; Talbot, J.; Hodges, R. S.; Ray,P. N.; Worton, R. G.: The Duchenne muscular dystrophy gene productis localized in sarcolemma of human skeletal

muscle. Nature 333:466–469, 1988.

[0446]   44.Alimova-Kost, M. V.; Imreh, S.; Buchman, V. L.; Nink-ina, N. N.: Assignment of phosphotriesterase-related gene (PTER) to human chromosomeband 10p12 by in situ hy-bridization. Cytogenet. Cell Genet. 83:16–17, 1998.

[0447]   45.Davies, J. A.; Buchman, V. L.; Krylova, O.; Ninkina, N. N.: Molecularcloning and expression pattern of rpr-1, a resiniferatoxin-binding,phosphotriesterase-related pro-tein, expressed in rat kidney tubules. FEBSLett. 410: 378–382, 1997.

[0448]   46.Ishikawa, K.; Nagase, T.; Nakajima, D.; Seki, N.; Ohira, M.; Miyajima,N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O.: Prediction ofthe coding sequences of unidenti-fied human genes. VIII. 78 new cDNAclones from brain which code for large proteins in vitro. DNA Res. 4:307–313, 1997.

[0449]   47.Duilio, A.; Faraonio, R.; Minopoli, G.; Zambrano, N.; Russo, T.: Fe65L2: a new member of the Fe65 protein family interacting withthe intracellular domain of the Alzheimer's beta-amyloid precursorprotein. Biochem. J. 330: 513–519, 1998.

[0450]   48.Tanahashi, H.; Tabira, T.: Genome structure and chro-mosomal mappingof the gene for Fe65L2 interacting with

Alzheimer's beta-amyloid precursorprotein. Biochem. Biophys. Res. Commun. 258: 385-389, 1999.

[0451] 49.Tanahashi, H.; Tabira, T.: Molecular cloning of human Fe65L2 andits interaction with the Alzheimer's beta-amyloid precursor protein. Neurosci.Lett. 261: 143-146, 1999.

[0452] 50.Delon, J.; Kaibuchi, K.; Germain, R. N.: Exclusion of CD43 fromthe immunological synapse is mediated by phosphorylation-regulatedrelocation of the cytoskeletal adaptor moesin. Immunity 15: 691-701,2001.

[0453] 51.Nekrep, N.; Jabrane-Ferrat, N.; Wolf, H. M.; Eibl, M. M.; Geyer,M.; Peterlin, B. M.: Mutation in a winged-helix DNA-binding motifcauses atypical bare lymphocyte syndrome. Nature Immun. 30Sept,2002. Note: Advance Electronic Publication.

[0454] 52.Gervais, F. G.; Xu, D.; Robertson, G. S.; Vaillancourt, J. P.;Zhu, Y.; Huang, J.; LeBlanc, A.; Smith, D.; Rigby, M.; Shearman, M.S.; Clarke, E. E.; Zheng, H.; Van Der Ploeg, L. H. T.; Ruffolo, S.C.; Thornberry, N. A.; Xanthoudakis, S.; Zamboni, R. J.; Roy, S.;Nicholson, D. W.: Involvement of caspases in proteolytic cleavageof Alzheimer's amyloid-beta precursor protein and amyloidogenic A-betapeptide formation. Cell 97: 395-406, 1999.

[0455] 53.Orstavik, S.; Solberg, R.; Tasken, K.; Nordahl, M.; Al-therr, M.R.; Hansson, V.; Jahnsen, T.; Sandberg, M.: Molecular cloning, cDNAstructure, and chromosomal localization of the human type II cGMP-dependentprotein kinase. Biochem. Biophys. Res. Commun. 220: 759-765, 1996.

[0456] 54.Pfeifer, A.; Aszodi, A.; Seidler, U.; Ruth, P.; Hofmann, F.; Fassler,R.: Intestinal secretory defects and dwarfism in mice lacking cGMP-dependentprotein kinase II. Science 274: 2082-2084, 1996.

[0457] 55.Liu, N.; Schild, D.; Thelen, M. P.; Thompson, L. H.: Involvementof Rad51C in two distinct protein complexes of Rad51 paralogs in humancells. Nucleic Acids Res. 30: 1009-1015, 2002.

[0458] 56.Masson, J.-Y.; Tarsounas, M. C.; Stasiak, A. Z.; Stasiak, A.; Shah,R.; McIlwraith, M. J.; Benson, F. E.; West, S. C.: Identificationand purification of two distinct complexes containing the five RAD51paralogs. Genes Dev. 15: 3296-3307, 2001.

[0459] 57.Isnard, P.; Depetris, D.; Mattei, M.-G.; Ferrier, P.; Dja-bali,M.: cDNA cloning, expression and chromosomal localization of themurine AF-4 gene involved in human leukemia. Mammalian Genome 9:1065-1068, 1998.

[0460] 58.Lovett, B. D.; Lo Nigro, L.; Rappaport, E. F.; Blair, I. A.; Osheroff,N.; Zheng, N.; Megonigal, M. D.; Williams, W. R.; Nowell, P. C.; Felix,C. A.: Near-precise interchromosomal recombination and functionalDNA topoisomerase II cleavage sites at MLL and AF-4 genomic breakpointsin treatment-related acute lymphoblastic leukemia with t(4;11) translocation. Proc.Nat. Acad. Sci. 98: 9802-9807, 2001.

[0461] 59.Uckun, F. M.; Herman-Hatten, K.; Crotty, M.-L.; Sensel, M. G.;Sather, H. N.; Tuel-Ahlgren, L.; Sarquis, M. B.; Bostrom, B.; Nachman,J. B.; Steinherz, P. G.; Gaynon, P. S.; Heerema, N.: Clinical significanceof MLL-AF4 fusion transcript expression in the absence of a cytogeneticallydetectable t(4;11)(q21;q23) chromosomal translocation. Blood 92:810-821, 1998.

[0462] 60.Huh, G. S.; Boulanger, L. M.; Du, H.; Riquelme, P. A.; Brotz, T.M.; Shatz, C. J.: Functional requirement for class I MHC in CNS developmentand plasticity. Science 290: 2155-2159, 2000.

[0463] 61.Qian, F.; Kruse, U.; Lichter, P.; Sippel, A. E.: Chromosomal localizationof the four genes (NFIA, B, C, and X) for the human transcriptionfactor nuclear factor I by FISH. Genomics 28: 66-73, 1995.

[0464] 62.Engelender, S.; Kaminsky, Z.; Guo, X.; Sharp, A. H.;

Amaravi, R.K.; Kleiderlein, J. J.; Margolis, R. L.; Troncoso, J. C.; Lanahan,A. A.; Worley, P. F.; Dawson, V. L.; Dawson, T. M.; Ross, C. A.:Synphilin-1 associates with alpha-synuclein and promotes the formationof cytosolic inclusions. Nature Genet. 22: 110-114, 1999.

[0465] 63.Amiel, J.; Salomon, R.; Attie, T.; Pelet, A.; Trang, H.; Mokhtari,M.; Gaultier, C.; Munnich, A.; Lyonnet, S.: Mutations of the RET-GDNFsignaling pathway in Ondine's curse. (Letter) Am. J. Hum. Genet. 62:715-717, 1998.

[0466] 64.Angrist, M.; Bolk, S.; Thiel, B.; Puffenberger, E. G.; Hofstra,R. M.; Buys, C. H. C. M.; Cass, D. T.; Chakravarti, A.: Mutationanalysis of the RET receptor tyrosine kinase in Hirschsprung disease. Hum.Molec. Genet. 4: 821-830, 1995.

[0467] 65.Antinolo, G.; Marcos, I.; Fernandez, R. M.; Romero, M.; Borrego,S.: A novel germline point mutation, c.2304G(T, in codon 768 of theRET proto-oncogene in a patient with medullary thyroid carcinoma.(Letter) Am. J. Med. Genet. 110: 85-87, 2002.

[0468] 66.Attie, T.; Pelet, A.; Edery, P.; Eng, C.; Mulligan, L. M.; Amiel,J.; Boutrand, L.; Beldjord, C.; Nihoul-Fekete, C.; Munnich, A.; Ponder,B. A. J.; Lyonnet, S.: Diversity of RET proto-oncogene mutationsin familial and sporadic

Hirschsprung disease. Hum. Molec. Genet. 4:1381–1386, 1995.

[0469] 67.Attie-Bitach, T.; Abitbol, M.; Gerard, M.; Delezoide, A.-L.; Auge,J.; Pelet, A.; Amiel, J.; Pachnis, V.; Munnich, A.; Lyonnet, S.; Vekemans,M.: Expression of the RET proto-oncogene in human embryos. Am. J.Med. Genet. 80: 481–486, 1998.

[0470] 68.Auricchio, A.; Griseri, P.; Carpentieri, M. L.; Betsos, N.; Staiano,A.; Tozzi, A.; Priolo, M.; Thompson, H.; Bocciardi, R.; Romeo, G.;Ballabio, A.; Ceccherini, I.: Double heterozy-gosity for a RET substitutioninterfering with splicing and an EDNRB missense mutation in Hirschsprungdisease. (Letter) Am. J. Hum. Genet. 64: 1216–1221, 1999.

[0471] 69.Batourina, E.; Choi, C.; Paragas, N.; Bello, N.; Hensle, T.; Costantini,F. D.; Schuchardt, A.; Bacallao, R. L.; Mendelsohn, C. L.: Distalureter morphogenesis depends on epithelial cell remodeling mediatedby vitamin A and Ret. Nature Genet. 32: 109–115, 2002. Note: Erra-tum:Nature Genet. 32: 331 only, 2002.

[0472] 70.Batourina, E.; et al; et al: Vitamin A controls epithelial/mesenchymalinteractions through Ret expression. Nature Genet. 27: 74–78, 2001.

[0473] 71.Berndt, I.; Reuter, M.; Saller, B.; Frank-Raue, K.; Groth,

P.:Grubendorf, M.; Raue, F.; Ritter, M. M.; Hoppner, W.: A new hot spotfor mutations in the ret protooncogene causing familial medullarythyroid carcinoma and multiple endocrine neoplasia type 2A. J. Clin.Endocr. Metab. 83: 770-774, 1998.

[0474] 72.Boccia, L. M.; Green, J. S.; Joyce, C.; Eng, C.; Taylor, S. A.M.; Mulligan, L. M.: Mutation of RET codon 768 is associated withthe FMTC phenotype. Clin. Genet. 51: 81-85, 1997.

[0475] 73.Bolino, A.; Schuffenecker, I.; Luo, Y.; Seri, M.; Silengo, M.;Tocco, T.; Chabrier, G.; Houdent, C.; Murat, A.; Schlumberger, M.;Tourniaire, J.; Lenoir, G. M.; Romeo, G.: RET mutations in exons13 and 14 of FMTC patients. Oncogene 10: 2415-2419, 1995.

[0476] 74.Bolk, S.; Angrist, M.; Schwartz, S.; Silvestri, J. M.; Weese-Mayer,D. E.; Chakravarti, A.: Congenital central hypoventilation syndrome:mutation analysis of the receptor tyrosine kinase RET. Am. J. Med.Genet. 63: 603-609, 1996.

[0477] 75.Bolk Gabriel, S.; Salomon, R.; Pelet, A.; Angrist, M.; Amiel,J.; Fornage, M.; Attie-Bitach, T.; Olson, J. M.; Hofstra, R.; Buys,C.; Steffann, J.; Munnich, A.; Lyonnet, S.; Chakravarti, A.: Segregationat three loci explains familial

and population risk in Hirschsprungdisease. Nature Genet. 31: 89-93, 2002.

[0478] 76.Ceccherini, I.; Hofstra, R. M.; Luo, Y.; Stulp, R. P.; Barone,V.; Stelwagen, T.; Bocciardi, R.; Nijveen, H.; Bolino, A.; Seri, M.;Ronchetto, P.; Pasini, B.; Bozzano, M.; Buys, C. H. C. M.; Romeo,G.: DNA polymorphisms and conditions for SSCP analysis of the 20exons of the Ret proto-oncogene. Oncogene 9: 3025-3029, 1994.

[0479] 77.Puffenberger, E. G.; Hosoda, K.; Washington, S. S.; Nakao, K.;deWit, D.; Yanagisawa, M.; Chakravarti, A.: A missense mutation ofthe endothelin-B receptor gene in multigenic Hirschsprung's disease. Cell 79:1257-1266, 1994.

[0480] 78.Svensson, P.-J.; Anvret, M.; Molander, M.-L.; Norden-skjold, A.: Phenotypic variation in a family with mutations in two Hirschsprung-relatedgenes (RET and endothelin re-ceptor B). Hum. Genet. 103: 145-148,1998.

[0481] 79.Lipinski, M.; Virelizier, J. L.; Tursz, T.; Griscelli, C.: Nat-uralkiller and killer cell activities in patients with primary immunodeficienciesor defects in immune interferon pro-duction. Europ. J. Immun. 10:246-249, 1980.

[0482] 80.Walder, K.; Norman, R. A.; Hanson, R. L.; Schrauwen, P.; Neverova,M.; Jenkinson, C. P.; Easlick, J.; Warden, C. H.;

Pecqueur, C.; Raimbault,S.; Ricquier, D.; Harper, M.; Silver, K.; Shuldiner, A. R.; Solanes,G.; Lowell, B. B.; Chung, W. K.; Leibel, R. L.; Pratley, R.; Ravussin,E.: Association between uncoupling protein polymorphisms (UCP2-UCP3)and energy metabolism/obesity in Pima Indians. Hum. Molec. Genet. 7:1431-1435, 1998.

[0483] 81.Hagiwara, T.; Tanaka, K.; Takai, S.; Maeno-Hikichi, Y.; Mukainaka,Y.; Wada, K.: Genomic organization, promoter analysis, and chromosomallocalization of the gene for the mouse glial high-affinity glutamatetransporter Slc1a3. Genomics 33: 508-515, 1996.

[0484] 82.Harada, T.; Harada, C.; Watanabe, M.; Inoue, Y.; Sakagawa, T.;Nakayama, N.; Sasaki, S.; Okuyama, S.; Watase, K.; Wada, K.; Tanaka,K.: Functions of the two glutamate transporters GLAST and GLT-1 inthe retina. Proc. Nat. Acad. Sci. 95: 4663-4666, 1998.

[0485] 83.Keppen, L. D.; Gollin, S. M.; Edwards, D.; Sawyer, J.; Wilson,W.; Overhauser, J.: Clinical phenotype and molecular analysis ofa three-generation family with an interstitial deletion of the shortarm of chromosome 5. Am. J. Med. Genet. 44: 356-360, 1992.

[0486] 84.Kirschner, M. A.; Arriza, J. L.; Copeland, N. G.; Gilbert, D. J.;Jenkins, N. A.; Magenis, E.; Amara, S. G.: The mouse

and human excitatoryamino acid transporter gene (EAAT1) maps to mouse chromosome 15 anda region of syntenic homology on human chromosome 5. Genomics 22:631–633, 1994.

[0487] 85.Shashidharan, P.; Huntley, G. W.; Meyer, T.; Morrison, J. H.; Plaitakis,A.: Neuron-specific human glutamate transporter: molecular cloning,characterization and expression in human brain. Brain Res. 662:245–250, 1994.

[0488] 86.Stoffel, W.; Sasse, J.; Duker, M.; Muller, R.; Hofmann, K.; Fink,T.; Lichter, P.: Human high affinity, Na(+)-dependent L-glutamate/L-aspartatetransporter GLAST-1 (EAAT-1): gene structure and localization to chromosome5p11-p12. FEBS Lett. 386: 189–193, 1996.

[0489] 87.Takai, S.; Yamada, K.; Kawakami, H.; Tanaka, K.; Nakamura, S.:Localization of the gene (SLC1A3) encoding human glutamate transporter(GluT-1) to 5p13 by fluorescence in situ hybridization. Cytogenet.Cell Genet. 69: 209–210, 1995.

[0490] 88.Hu, X.; Burghes, A. H. M.; Ray, P. N.; Thompson, M. W.; Murphy,E. G.; Worton, R. G.: Partial gene duplication in Duchenne and Beckermuscular dystrophies. J. Med. Genet. 25: 369–376, 1988.

[0491] 89.Bucan, M.; Gatalica, B.; Nolan, P.; Chung, A.; Leroux,

A.; Grossman,M. H.; Nadeau, J. H.; Emanuel, B. S.; Budarf, M.: Comparative mappingof 9 human chromosome 22q loci in the laboratory mouse. Hum. Molec.Genet. 2: 1245-1252, 1993.

[0492] 90.Cetta, F.; Chiappetta, G.; Melillo, R. M.; Petracci, M.; Montalto,G.; Santoro, M.; Fusco, A.: The ret/ptc1 onco-gene is activated infamilial adenomatous polyposis-associated thyroid papillary carcinomas. J.Clin. Endocr. Metab. 83: 1003-1006, 1998.

[0493] 91.Decker, R. A.; Peacock, M. L.; Watson, P.: Hirschsprung diseasein MEN 2A: increased spectrum of RET exon 10 genotypes and stronggenotype-phenotype correlation. Hum. Molec. Genet. 7: 129-134, 1998.

[0494] 92.Donis-Keller, H.; Dou, S.; Chi, D.; Carlson, K. M.; Toshima, K.;Lairmore, T. C.; Howe, J. R.; Moley, J. F.; Goodfellow, P.; Wells,S. A., Jr.: Mutations in the RET proto-oncogene are associated withMEN 2A and FMTC. Hum. Molec. Genet. 2: 851-856, 1993.

[0495] 93.Doray, B.; Salomon, R.; Amiel, J.; Pelet, A.; Touraine, R.; Billaud,M.; Attie, T.; Bachy, B.; Munnich, A.; Lyonnet, S.: Mutation of theRET ligand, neurturin, supports multigenic inheritance in Hirschsprungdisease. Hum. Molec. Genet. 7: 1449-1452, 1998.

[0496] 94.Edery, P.; Lyonnet, S.; Mulligan, L. M.; Pelet, A.; Dow, E.; Abel,L.; Holder, S.; Nihoul-Fekete, C.; Ponder, B. A. J.; Munnich, A.:Mutations of the RET proto-oncogene in Hirschsprung's disease. Nature 367:378-380, 1994.

[0497] 95.Eng, C.: The RET proto-oncogene in multiple endocrine neoplasiatype 2 and Hirschsprung's disease. New Eng. J. Med. 335: 943-951,1996.

[0498] 96.Eng, C.; Crossey, P. A.; Mulligan, L. M.; Healey, C. S.; Houghton,C.; Prowse, A.; Chew, S. L.; Dahia, P. L. M.; O'Riordan, J. L. H.;Toledo, S. P. A.; Smith, D. P.; Maher, E. R.; Ponder, B. A. J.: Mutationsin the RET proto-oncogene and the von Hippel-Lindau disease tumoursuppressor gene in sporadic and syndromic phaeochromocytomas. J.Clin. Genet. 32: 934-937, 1995.

[0499] 97.Eng, C.; Mulligan, L. M.: Mutations of the RET proto-oncogenein the multiple endocrine neoplasia type 2 syn-dromes, related sporadictumours, and Hirschsprung dis-ease. Hum. Mutat. 9: 97-109, 1997.

[0500] 98.Eng, C.; Mulligan, L. M.; Smith, D. P.; Healey, C. S.; Frilling,A.; Raue, F.; Neumann, H. P. H.; Pfragner, R.; Behmel, A.; Lorenzo,M. J.; Stonehouse, T. J.; Ponder, M. A.; Ponder, B. A. J.: Mutationof the RET protooncogene in sporadic medullary thyroid carcinoma. GenesChromo-

somes Cancer 12: 209–212, 1995.

[0501] 99.Eng, C.; Smith, D. P.; Mulligan, L. M.; Healey, C. S.; Zvelebil,M. J.; Stonehouse, T. J.; Ponder, M. A.; Jackson, C. E.; Waterfield,M. D.; Ponder, B. A. J.: A novel point mutation in the tyrosine kinasedomain of the RET proto-oncogene in sporadic medullary thyroid carcinomaand in a family with FMTC. Oncogene 10: 509–513, 1995.

[0502] 100.Eng, C.; Smith, D. P.; Mulligan, L. M.; Nagai, M. A.; Healey,C. S.; Ponder, M. A.; Gardner, E.; Scheumann, G. F. W.; Jackson, C.E.; Tunnacliffe, A.; Ponder, B. A. J.: Point mutation within thetyrosine kinase domain of the RET proto-oncogene in multiple endocrineneoplasia type 2B and related sporadic tumors. Hum. Molec. Genet. 3:237–241, 1994.

[0503] 101.Fearon, E. R.: Human cancer syndromes: clues to the origin andnature of cancer. Science 278: 1043–1050, 1997.

[0504] 102.Fitze, G.; Schreiber, M.; Kuhlisch, E.; Schackert, H. K.; Roesner,D.: Association of RET protooncogene codon 45 polymorphism with Hirschsprungdisease. (Letter) Am. J. Hum. Genet. 65: 1469–1473, 1999.

[0505] 103.Gardner, E.; Mulligan, L. M.; Eng, C.; Healey, C. S.; Kwok, J.B. J.; Ponder, M. A.; Ponder, B. A. J.: Haplotype

analysis of MEN2 mutations. Hum. Molec. Genet. 3: 1771-1774, 1994.

[0506] 104.Grieco, M.; Santoro, M.; Berlingieri, M. T.; Melillo, R. M.; Donghi,R.; Bongarzone, I.; Pierotti, M. A.; Della Porta, G.; Fusco, A.; Vecchio,G.: PTC is a novel rearranged form of the ret proto-oncogene andis frequently detected in vivo in human thyroid papillary carcinomas. Cell 60:557-563, 1990.

[0507] 105.Hofstra, R. M. W.; Landsvater, R. M.; Ceccherini, I.; Stulp, R.P.; Stelwagen, T.; Luo, Y.; Pasini, B.; Hoppener, J. W. M.; Ploosvan Amstel, H. K.; Romeo, G.; Lips, C. J. M.; Buys, C. H. C. M.:A mutation in the RET proto-oncogene associated with multiple endocrineneoplasia type 2B and sporadic medullary thyroid carcinoma. Nature 367:375-376, 1994.

[0508] 106.Hoppener, J. W. M.; Lips, C. J. M.: RET receptor tyro-sine kinasegene mutations: molecular biological, physio-logical and clinical aspects. Europ.J. Clin. Invest. 26: 613-624, 1996.

[0509] 107.Hoppner, W.; Ritter, M. M.: A duplication of 12 bp in the criticalcysteine rich domain of the RET proto-oncogene results in a distinctphenotype of multiple en-docrine neoplasia type 2A. Hum. Molec. Genet.

6:587-590, 1997.

[0510] 108.Ikeda, I.; Ishizaka, Y.; Tahira, T.; Suzuki, T.; Onda, M.; Sugimura,T.; Nagao, M.: Specific expression of the ret proto-oncogene in humanneuroblastoma cell lines. Oncogene 5: 1291-1296, 1990.

[0511] 109.Ishizaka, Y.; Itoh, F.; Tahira, T.; Ikeda, I.; Sugimura, T.; Tucker,J.; Fertitta, A.; Carrano, A. V.; Nagao, M.: Human ret proto-oncogenemapped to chromosome 10q11.2. Oncogene 4: 1519-1521, 1989.

[0512] 110.Japon, M. A.; Urbano, A. G.; Saez, C.; Segura, D. I.; Cerro, A.L.; Dieguez, C.; Alvarez, C. V.: Glial-derived neurotropic factorand RET gene expression in normal human anterior pituitary cell typesand in pituitary tumors. J. Clin. Endocr. Metab. 87: 1879-1884,2002.

[0513] 111.Julies, M. G.; Moore, S. W.; Kotze, M. J.; du Plessis, L.: NovelRET mutations in Hirschsprung's disease patients from the diverseSouth African population. Europ. J. Hum. Genet. 9: 419-423, 2001.

[0514] 112.Klugbauer, S.; Demidchik, E. P.; Lengfelder, E.; Rabes, H. M.: Detection of a novel type of RET rearrangement (PTC5) in thyroidcarcinomas after Chernobyl and analysis of the involved RET-fusedgene RFG5. Cancer Res. 58: 198-203, 1998.

[0515] 113.Allikmets, R.; Seddon, J. M.; Bernstein, P. S.; Hutchinson, A.;Atkinson, A.; Sharma, S.; Gerrard, B.; Li, W.; Metzker, M. L.; Wadelius,C.; Caskey, C. T.; Dean, M.; Petrukhin, K.: Evaluation of the Bestdisease gene in patients with age-related macular degeneration andother maculopathies. Hum. Genet. 104: 449-453, 1999.

[0516] 114.Bascom, R. A.; Liu, L.; Chen, J.; Duncan, A.; Kimberling, W. J.;Moller, C. G.; Humphries, P.; Nathans, J.; McInnes, R. R.: ROM1:a candidate gene for autosomal dominant retinitis pigmentosa (ADRP),Usher syndrome type 1, and Best vitelliform macular dystrophy. (Abstract) Am.J. Hum. Genet. 51 (suppl.): A6, 1992.

[0517] 115.Best, F.: Ueber eine hereditaere Maculaaffektion. Z. Augenheilk. 13:199-212, 1905.

[0518] 116.Braley, A. E.: Dystrophy of the macula. Am. J. Ophthal. 61:1-24, 1966.

[0519] 117.Braley, A. E.; Spivey, B. E.: Hereditary vitelline macular degeneration:a clinical and functional evaluation of a new pedigree with variableexpressivity and dominant inheritance. Arch. Ophthal. 72: 743-762,1964.

[0520] 118.Brecher, R.; Bird, A. C.: Adult vitelliform macular dystrophy. Eye 4:210-215, 1990.

[0521] 119.Davis, C. T.; Hollenhorst, R. W.: Hereditary degenera-

tion of themacula: occurring in five generations. Am. J. Ophthal. 39: 637-643,1955.

[0522] 120.Deutman, A. F.: Electro-oculography in families with vitelliformdystrophy of the fovea: detection of the carrier state. Arch. Ophthal. 81:305-316, 1969.

[0523] 121.Falls, H. F.: Hereditary congenital macular degeneration. Am.J. Hum. Genet. 1: 96-104, 1949.

[0524] 122.Forsman, K.; Graff, C.; Nordstrom, S.; Johansson, K.; Westermark,E.; Lundgren, E.; Gustavson, K.-H.; Wadelius, C.; Holmgren, G.: Thegene for Best's macular dystrophy is located at 11q13 in a Swedishfamily. Clin. Genet. 42: 156-159, 1992.

[0525] 123.Francois, J.: Vitelliform degeneration of the macula. Bull.N.Y. Acad. Med. 44: 18-27, 1968.

[0526] 124.Friedenwald, J. S.; Maumenee, A. E.: Peculiar macular lesionswith unaccountably good vision. Arch. Ophthal. 45: 567-570, 1951.

[0527] 125.Goodstadt, L.; Ponting, C. P.: Sequence variation and diseasein the wake of the draft human genome. Hum. Molec. Genet. 10: 2209-2214,2001.

[0528] 126.Graff, C.; Eriksson, A.; Forsman, K.; Sandgren, O.; Holmgren,G.; Wadelius, C.: Refined genetic localization of the Best diseasegene in 11q13 and physical mapping of

linked markers on radiationhybrids. Hum. Genet. 101: 263-270, 1997.

[0529] 127.Graff, C.; Forsman, K.; Larsson, C.; Nordstrom, S.; Lind, L.;Johansson, K.; Sandgren, O.; Weissenbach, J.; Holmgren, G.; Gustavson,K.-H.; Wadelius, C.: Fine mapping of Best's macular dystrophy localizesthe gene in close proximity to but distinct from the D11S480/ROM1loci. Genomics 24: 425-434, 1994.

[0530] 128.Hagemeijer, A.; Hoovers, J.; Smit, E. M. E.; Bootsma, D.: Replicationpattern of the X chromosomes in three X/ autosomal translocations. Cytogenet.Cell Genet. 18: 333-348, 1977.

[0531] 129.Hou, Y.-C.; Richards, J. E.; Bingham, E. L.; Pawar, H.; Scott,K.; Segal, M.; Lunetta, K. L.; Boehnke, M.; Sieving, P. A.: Linkagestudy of Best's vitelliform macular dystrophy (VMD2) in a large NorthAmerican family. Hum. Hered. 46: 211-220, 1996.

[0532] 130.Jung, E. E.: Ueber eine Sippe mit angeborener Maculadegeneration. Giessen: Seibert (pub.) 1936.

[0533] 131.Bandmann, O.; Davis, M. B.; Marsden, C. D.; Wood, N. W.: The humanhomologue of the weaver mouse gene in familial and sporadic Parkinson'sdisease. Neuroscience 72: 877-879, 1996.

[0534] 132.Domer, P. H.; Fakharzadeh, S. S.; Chen, C.-S.; Jockel, J.; Johansen,L.; Silverman, G. A.; Kersey, J. H.; Korsmeyer, S. J.: Acute mixed-lineageleukemia t(4;11)(q21;q23) generates an MLL-AF4 fusion product. Proc.Nat. Acad. Sci. 90: 7884-7888, 1993.

[0535] 133.Gu, Y.; Nakamura, T.; Alder, H.; Prasad, R.; Canaani, O.; Cimino,G.; Croce, C. M.; Canaani, E.: The t(4;11) chromosome translocationof human acute leukemias fuses the ALL-1 gene, related to Drosophilatrithorax, to the AF-4 gene. Cell 71: 701-708, 1992.

[0536] 134.Nakamura, T.; Alder, H.; Gu, Y.; Prasad, R.; Canaani, O.; Kamada,N.; Gale, R. P.; Lange, B.; Crist, W. M.; Nowell, P. C.; Croce, C.M.; Canaani, E.: Genes on chromosomes 4, 9, and 19 involved in 11q23abnormalities in acute leukemia share sequence homology and/or commonmotifs. Proc. Nat. Acad. Sci. 90: 4631-4635, 1993.

[0537] 135.Adkison, L. R.; White, R. A.; Haney, D. M.; Lee, J. C.; Pusey,K. T.; Gardner, J.: The fibronectin receptor, alpha subunit (Itga5)maps to murine chromosome 15, distal to D15Mit16. Mammalian Genome 5:456-457, 1994.

[0538] 136.Argraves, W. S.; Pytela, R.; Suzuki, S.; Millan, J. L.; Pierschbacher,M. D.; Ruoslahti, E.: cDNA sequences from the alpha subunit of thefibronectin receptor predict a

transmembrane domain and a short cytoplasmicpeptide. J. Biol. Chem. 261: 12922-12924, 1986.

[0539] 137.Argraves, W. S.; Suzuki, S.; Arai, H.; Thompson, K.; Pierschbacher,M. D.; Ruoslahti, E.: Amino acid sequence of the human fibronectinreceptor. J. Cell Biol. 105: 1183-1190, 1987.

[0540] 138.Fitzgerald, L. A.; Poncz, M.; Steiner, B.; Rall, S. C., Jr.; Bennett,J. S.; Phillips, D. R.: Comparison of cDNA-derived protein sequencesof the human fibronectin and vit-ronectin receptor alpha-subunits andplatelet glycoprotein IIb. Biochemistry 26: 8158-8165, 1987.

[0541] 139.Krissansen, G. W.; Yuan, Q.; Jenkins, D.; Jiang, W.-M.; Rooke,L.; Spurr, N. K.; Eccles, M.; Leung, E.; Watson, J. D.: Chromosomallocations of the genes coding for the inte-grin beta-6 and beta-7 subunits. Immunogenetics 35:58-61, 1992.

[0542] 140.Sosnoski, D.; Emanuel, B. S.; Hawkins, A. L.; van Tu-inen, P.; Ledbetter,D. H.; Nussbaum, R. L.; Kaos, F.-T.; Schwartz, E.; Phillips, D.; Bennett,J. S.; Fitzgerald, L. A.; Poncz, M.: Chromosomal localization ofthe genes for the vitronectin and fibronectin receptors alpha-subunitsand for platelet glycoproteins IIb and IIIa. J. Clin. Invest. 81:1993-1998, 1988.

[0543] 141.Spurr, N. K.; Rooke, L.: Confirmation of the assignment of thevitronectin (VNRA) and fibronectin (FNRA) receptor alpha-subunits. Ann.Hum. Genet. 55: 217-223, 1991.

[0544] 142.Klugbauer, S.; Rabes, H. M.: The transcription coactivator HTIF1and a related protein are fused to the RET receptor tyrosine kinasein childhood papillary thyroid carcinomas. Oncogene 18: 4388-4393,1999.

[0545] 143.Lairmore, T. C.; Dou, S.; Howe, J. R.; Chi, D.; Carlson, K.; Veile,R.; Mishra, S. K.; Wells, S. A., Jr.; Donis-Keller, H.: A 1.5-megabaseyeast artificial chromosome contig from human chromosome 10q11.2 connectingthree genetic loci (RET, D10S94, and D10S102) closely linked to theMEN2A locus. Proc. Nat. Acad. Sci. 90: 492-496, 1993.

[0546] 144.Lombardo, F.; Baudin, E.; Chiefari, E.; Arturi, F.; Bardet, S.;Caillou, B.; Conte, C.; Dallapiccola, B.; Giuffrida, D.; Bidart, J.-M.;Schlumberger, M.; Filetti, S.: Familial medullary thyroid carcinoma:clinical variability and low aggressiveness associated with RET mutationat codon 804. J. Clin. Endocr. Metab. 87: 1674-1680, 2002.

[0547] 145.Lore, F.; Di Cairano, G.; Talidis, F.: Unilateral renal agenesisin a family with medullary thyroid carcinoma. (Letter) New Eng. J.Med. 342: 1218-1219, 2000.

[0548] 146.Machens, A.; Gimm, O.; Hinze, R.; Hoppner, W.; Boehm, B. O.; Dralle,H.: Genotype-phenotype correlations in hereditary medullary thyroidcarcinoma: oncological features and biochemical properties. J. Clin.Endocr. Metab. 86: 1104-1109, 2001.

[0549] 147.Mendelsohn, C.; et al; et al: Function of the retinoic acid receptors(RARs) during development (II). Multiple abnormalities at variousstages of organogenesis in RAR double mutants. Development 120:2749-2771, 1994.

[0550] 148.Menko, F. H.; van der Luijt, R. B.; de Valk, I. A. J.; Toorians,A. W. F. T.; Sepers, J. M.; van Diest, P. J.; Lips, C. J. M.: AtypicalMEN type 2B associated with two germline RET mutations on the sameallele not involving codon 918. J. Clin. Endocr. Metab. 87: 393-397,2002.

[0551] 149.Mulligan, L. M.; Kwok, J. B. J.; Healey, C. S.; Elsdon, M. J.;Eng, C.; Gardner, E.; Love, D. R.; Mole, S. E.; Moore, J. K.; Papi,L.; Ponder, M. A.; Telenius, H.; Tunnacliffe, A.; Ponder, B. A. J.: Germ-line mutations of the RET proto-oncogene in multiple endocrineneoplasia type 2A. Nature 363: 458-460, 1993.

[0552] 150.Munnes, M.; Fanaei, S.; Schmitz, B.; Muiznieks, I.; Holschneider,A. M.; Doerfler, W.: Familial form of Hirschsprung disease: nucleotidesequence studies reveal

point mutations in the RET proto-oncogenein two of six families but not in other candidate genes. Am. J. Med.Genet. 94: 19–27, 2000.

[0553]   151.Nakata, T.; Kitamura, Y.; Shimizu, K.; Tanaka, S.; Fuji-mori, M.;Yokoyama, S.; Ito, K.; Emi, M.: Fusion of a novel gene, ELKS, toRET due to translocation t(10;12)(q11;p13) in a papillary thyroidcarcinoma. Genes Chromosomes Cancer 25: 97–103, 1999.

[0554]   152.Niccoli-Sire, P.; Murat, A.; Rohmer, V.; Franc, S.; Chabrier,G.; Baldet, L.; Maes, B.; Savagner, F.; Giraud, S.; Bezieau, S.; Kottler,M.-L.; Morange, S.; Conte-Devolx, B.: The French Calcitonin TumorsStudy Group (GETC).: Famil-ial medullary thyroid carcinoma with noncysteineRET mu-tations: phenotype-genotype relationship in a large series ofpatients. J. Clin. Endocr. Metab. 86: 3746–3753, 2001.

[0555]   153.Pachnis, V.; Mankoo, B.; Costantini, F.: Expression of the c-retproto-oncogene during mouse embryogenesis. Development 119: 1005–1017,1993.

[0556]   154.Pasini, B.; Hofstra, R. M. W.; Yin, L.; Bocciardi, R.; San-tamaria,G.; Grootscholten, P. M.; Ceccherini, I.; Patrone, G.; Priolo, M.;Buys, C. H. C. M.; Romeo, G.: The physical map of the human RET proto-oncogene. Oncogene 11:1737–1743, 1995.

[0557]   155.Pelet, A.; Geneste, O.; Edery, P.; Pasini, A.; Chappuis, S.; Attie,T.; Munnich, A.; Lenoir, G.; Lyonnet, S.; Billaud, M.: Various mechanismscause RET-mediated signaling defects in Hirschsprung's disease. J.Clin. Invest. 101: 1415-1423, 1998.

[0558]   156.Pigny, P.; Bauters, C.; Wemeau, J.-L.; Houcke, M. L.; Crepin,M.; Caron, P.; Giraud, S.; Calender, A.; Buisine, M.-P.; Kerckaert,J.-P.; Porchet, N.: A novel 9-base pair duplication in RET exon 8in familial medullary thyroid carcinoma. J. Clin. Endocr. Metab. 84:1700-1704, 1999.

[0559]   157.Pierotti, M. A.; Santoro, M.; Jenkins, R. B.; Sozzi, G.; Bongarzone,I.; Grieco, M.; Monzini, N.; Miozzo, M.; Herrmann, M. A.; Fusco, A.;Hay, I. D.; Della Porta, G.; Vecchio, G.: Characterization of aninversion on the long arm of chromosome 10 juxtaposing D10S170 andRET and creating the oncogenic sequence RET/PTC. Proc. Nat. Acad.Sci. 89: 1616-1620, 1992.

[0560]   158.Rodrigues, G. A.; Park, M.: Dimerization mediated through a leucinezipper activates the oncogenic potential of the met receptor tyrosinekinase. Molec. Cell. Biol. 13: 6711-6722, 1993.

[0561]   159.Romeo, G.; Ronchetto, P.; Luo, Y.; Barone, V.; Seri, M.; Ceccherini,I.; Pasini, B.; Bocciardi, R.; Lerone, M.; Kaari-

ainen, H.; Martucciello,G.: Point mutations affecting the tyrosine kinase domain of the RETproto-oncogene in Hirschsprung's disease. Nature 367: 377-378, 1994.

[0562] 160.Salvatore, D.; Barone, M. V.; Salvatore, G.; Melillo, R. M.; Chiappetta,G.; Mineo, A.; Fenzi, G.; Vecchio, G.; Fusco, A.; Santoro, M.: Tyrosines1015 and 1062 are in vivo autophosphorylation sites in Ret and Ret-derivedoncoproteins. J. Clin. Endocr. Metab. 85: 3898-3907, 2000.

[0563] 161.Robinson, M. F.; Cote, G. J.; Nunziata, V.; Brandi, M. L.; Ferrer,J. P.; Martins Bugalho, M. J. G.; Almeida Ruas, M. M.; Chik, C.; Colantuoni,V.; Gagel, R. F.: Mutation of a specific codon of the RET proto-oncogenein the multiple endocrine neoplasia type 2A/cutaneous lichen amyloido-sissyndrome. (Abstract) Fifth International Workshop on Multiple EndocrineNeoplasia, Stockholm, Archipelago , 1994.

[0564] 162.Ceccherini, I.; Romei, C.; Barone, V.; Pacini, F.; Martino, E.;Loviselli, A.; Pinchera, A.; Romeo, G.: Identification of the cys634-to-tyrmutation of the RET proto-oncogene in a pedigree with multiple endocrineneoplasia type 2A and localized cutaneous lichen amyloidosis. J.Endocr. Invest. 17: 201-204, 1994.

[0565] 163.Echtay, K. S.; Roussel, D.; St-Pierre, J.; Jekabsons, M. B.; Cadenas,S.; Stuart, J. A.; Harper, J. A.; Roebuck, S. J.; Morrison, A.; Pickering,S.; Clapham, J. C.; Brand, M. D.: Superoxide activates mitochondrialuncoupling proteins. Nature 415: 96-99, 2002.

[0566] 164.Enerback, S.; Jacobsson, A.; Simpson, E. M.; Guerra, C.; Yamashita,H.; Harper, M.-E.; Kozak, L. P.: Mice lacking mitochondrial uncouplingprotein are cold-sensitive but not obese. Nature 387: 90-93, 1997.

[0567] 165.Borrego, S.; Ruiz, A.; Saez, M. E.; Gimm, O.; Gao, X.; Lopez-Alonso,M.; Hernandez, A.; Wright, F. A.; Antinolo, G.; Eng, C.: RET genotypescomprising specific haplotypes of polymorphic variants predisposeto isolated Hirschsprung disease. J. Med. Genet. 37: 572-578, 2000.

[0568] 166.Borrego, S.; Saez, M. E.; Ruiz, A.; Gimm, O.; Lopez-Alonso, M.;Antinolo, G.; Eng, C.: Specific polymorphisms in the RET proto-oncogeneare over-represented in pa-tients with Hirschsprung disease and mayrepresent loci modifying phenotypic expression. J. Med. Genet. 36:771-774, 1999.

[0569] 167.Beranova, M.; Oliveira, L. M. B.; Bedecarrats, G. Y.; Schipani,E.; Vallejo, M.; Ammini, A. C.; Quintos, J. B.; Hall, J. E.; Martin,K. A.; Hayes, F. J.; Pitteloud, N.; Kaiser, U. B.;

Crowley, W. F.,Jr.; Seminara, S. B.: Prevalence, phenotypic spectrum, and modesof inheritance of gonadotropin-releasing hormone receptor mutationsin idiopathic hypogonadotropic hypogonadism. J. Clin. Endocr. Metab. 86:1580-1588, 2001.

[0570] 168.Caron, P.; Chauvin, S.; Christin-Maitre, S.; Bennet, A.; Lahlou,N.; Counis, R.; Bouchard, P.; Kottler, M.-L.: Resistance of hypogonadicpatients with mutated GnRH receptor genes to pulsatile GnRH administration. J.Clin. Endocr. Metab. 84: 990-996, 1999.

[0571] 169.Costa, E. M. F.; Bedecarrats, G. Y.; Mendonca, B. B.; Arnhold,I. J. P.; Kaiser, U. B.; Latronico, A. C.: Two novel mutations inthe gonadotropin- releasing hormone receptor gene in Brazilian patientswith hypogonadotropic hypogonadism and normal olfaction. J. Clin.Endocr. Metab. 86: 2680-2686, 2001.

[0572] 170.de Roux, N.; Young, J.; Brailly-Tabard, S.; Misrahi, M.; Milgrom,E.; Schaison, G.: The same molecular defects of the gonadotropin-releasinghormone receptor determine a variable degree of hypogonadism in affectedkindred. J. Clin. Endocr. Metab. 84: 567-572, 1999.

[0573] 171.de Roux, N.; Young, J.; Misrahi, M.; Genet, R.; Chanson, P.; Schaison,G.; Milgrom, E.: A family with hypogo-

nadotropic hypogonadism andmutations in the go-nadotropin-releasing hormone receptor. New Eng.J. Med. 337: 1597-1602, 1997.

[0574] 172.Fan, N. C.; Jeung, E.-B.; Peng, C.; Olofsson, J. I.; Krisinger,J.; Leung, P. C. K.: The human gonadotropin-releasing hormone (GnRH)receptor gene: cloning, genomic organization and chromosomal assignment. Molec.Cell. Endocr. 103: R1-R6, 1994.

[0575] 173.Iwashita, T.; Murakami, H.; Asai, N.; Takahashi, M.: Mechanismof Ret dysfunction by Hirschsprung mutations affecting its extracellulardomain. Hum. Molec. Genet. 5: 1577-1580, 1996.

[0576] 174.Fan, N. C.; Peng, C.; Krisinger, J.; Leung, P. C. K.: The humangonadotropin-releasing hormone receptor gene: complete structure includingmultiple promoters, transcription initiation sites, and polyadenylationsignals. Molec. Cell. Endocr. 107: R1-R8, 1995.

[0577] 175.Grosse, R.; Schoneberg, T.; Schultz, G.; Gudermann, T.: Inhibitionof gonadotropin-releasing hormone receptor signaling by expressionof a splice variant of the human receptor. Molec. Endocr. 11: 1305-1318,1997.

[0578] 176.Kaiser, U. B.; Dushkin, H.; Altherr, M. R.; Beier, D. R.; Chin,W. W.: Chromosomal localization of the go-

nadotropin-releasing hormonereceptor gene to human chromosome 4q13.1-q21.1 and mouse chromosome5. Genomics 20: 506-508, 1994.

[0579] 177.Kakar, S. S.; Musgrove, L. C.; Devor, D. C.; Sellers, J. C.; Neill,J. D.: Cloning, sequencing, and expression of human gonadotropinreleasing hormone (GnRH) receptor. Biochem. Biophys. Res. Commun. 189:289-295, 1992.

[0580] 178.Kakar, S. S.; Neill, J. D.: The human gonadotropin-releasinghormone receptor gene (GNRHR) maps to chromosome band 4q13. Cytogenet.Cell Genet. 70: 211-214, 1995.

[0581] 179.Kottler, M.-L.; Chauvin, S.; Lahlou, N.; Harris, C. E.; Johnston,C. J.; Lagarde, J.-P.; Bouchard, P.; Farid, N. R.; Counis, R.: Anew compound heterozygous mutation of the gonadotropin-releasing hormonereceptor (L314X, Q106R) in a woman with complete hypogonadotropichypogonadism: chronic estrogen administration amplifies the gonadotropindefect. J. Clin. Endocr. Metab. 85: 3002-3008, 2000.

[0582] 180.Kottler, M.-L.; Counis, R.; Bouchard, P.: Mutations of the GnRHreceptor gene: a new cause of autosomal-recessive hypogonadotropichypogonadism. Arch. Med. Res. 30: 481-485, 1999.

[0583] 181.Kottler, M. L.; Lorenzo, F.; Bergametti, F.; Commer-con, P.; Souchier,C.; Counis, R.: Subregional mapping of the human gonadotropin-releasinghormone receptor (GnRH-R) gene to 4q between the markers D4S392 andD4S409. Hum. Genet. 96: 477-480, 1995.

[0584] 182.Layman, L. C.; Cohen, D. P.; Jin, M.; Xie, J.; Li, Z.; Reindollar,R. H.; Bolbolan, S.; Bick, D. P.; Sherins, R. R.; Duck, L. W.; Musgrove,L. C.; Sellers, J. C.; Neill, J. D.: Mutations in gonadotropin-releasinghormone receptor gene cause hypogonadotropic hypogonadism. (Letter) Nature-Genet. 18: 14-15, 1998.

[0585] 183.Leung, P. C. K.; Squire, J.; Peng, C.; Fan, N.; Hayden, M. R.;Olofsson, J. I.: Mapping of the gonadotropin-releasing hormone (GnRH)receptor gene to human chromosome 4q21.2 by fluorescence in situ hybridization. Mam-malianGenome 6: 309-310, 1995.

[0586] 184.Mason, A. J.; Hayflick, J. S.; Zoeller, R. T.; Young, W. S., III;Phillips, H. S.; Nikolics, K.; Seeburg, P. H.: A deletion truncatingthe gonadotropin-releasing hormone gene is responsible for hypogonadismin the 'hpg' mouse. Science 234: 1366-1371, 1986.

[0587] 185.Morrison, N.; Sellar, R. E.; Boyd, E.; Eidne, K. A.; Con-nor, J.M.: Assignment of the gene encoding the human

gonadotropin-releasinghormone receptor to 4q13.2-13.3 by fluorescence in situ hybridization. Hum.Genet. 93: 714-715, 1994.

[0588]   186.Pitteloud, N.; Boepple, P. A.; DeCruz, S.; Valkenburgh, S. B.;Crowley, W. F., Jr.; Hayes, F. J.: The fertile eunuch variant ofidiopathic hypogonadotropic hypogonadism: spontaneous reversal associatedwith a homozygous mutation in the gonadotropin-releasing hormone receptor. J.Clin. Endocr. Metab. 86: 2470-2475, 2001.

[0589]   187.Pralong, F. P.; Gomez, F.; Castillo, E.; Cotecchia, S.; Abuin,L.; Aubert, M. L.; Portmann, L.; Gaillard, R. C.: Complete hypogonadotropichypogonadism associated with a novel inactivating mutation of thegonadotropin-releasing hormone receptor. J. Clin. Endocr. Metab. 84:3811-3816, 1999.

[0590]   188.Szende, B.; Srkalovic, G.; Timar, J.; Mulchahey, J. J.; Neill,J. D.; Lapis, K.; Csikos, A.; Szepeshazi, K.; Schally, A. V.: Localizationof receptors for luteinizing hormone-releasing hormone in pancreaticand mammary cancer cells. Proc. Nat. Acad. Sci. 88: 4153-4156, 1991.

[0591]   189.Carrasquillo, M. M.; McCallion, A. S.; Puffenberger, E. G.; Kashuk,C. S.; Nouri, N.; Chakravarti, A.: Genome-wide association studyand mouse model identify interaction

between RET and EDNRB pathwaysin Hirschsprung disease. Nature Genet. 32: 237-244, 2002.

[0592] 190.Wolffe, A. P.: Transcriptional control: sinful repression. Nature 387:16-17, 1997.

[0593] 191.Allenspach, E. J.; Cullinan, P.; Tong, J.; Tang, Q.; Tesciuba,A. G.; Cannon, J. L.; Takahashi, S. M.; Morgan, R.; Burkhardt, J.K.; Sperling, A. I.: ERM-dependent movement of CD43 defines a novelprotein complex distal to the immunological synapse. Immunity 15:739-750, 2001.

[0594] 192.Fenster, S. D.; Chung, W. J.; Zhai, R.; Cases-Langhoff, C.; Voss,B.; Garner, A. M.; Kaempf, U.; Kindler, S.; Gundelfinger, E. D.; Garner,C. C.: Piccolo, a presynaptic zinc finger protein structurally relatedto Bassoon. Neuron 25: 203-214, 2000.

[0595] 193.Bak, M.; Hansen, C.; Henriksen, K. F.; Tommerup, N.: The humanhedgehog-interacting protein gene: structure and chromosome mappingto 4q31.21-q31.3. Cytogenet. Cell Genet. 92: 300-303, 2001.

[0596] 194.Chuang, P.-T.; McMahon, A. P.: Vertebrate hedgehog signallingmodulated by induction of a hedgehog-binding protein. Nature 397:617-621, 1999.

[0597] 195.Anand, R.; Lindstrom, J.: Chromosomal localization of seven neuronalnicotinic acetylcholine receptor subunit

genes in humans. Genomics 13:962-967, 1992.

[0598] 196.Armstrong, E.; Partanen, J.; Cannizzaro, L.; Huebner, K.; Alitalo,K.: Localization of the fibroblast growth factor receptor-4 geneto chromosome region 5q33-qter. Genes Chromosomes Cancer 4: 94-98,1992.

[0599] 197.Bange, J.; Prechtl, D.; Cheburkin, Y.; Specht, K.; Harbeck, N.;Schmitt, M.; Knyazeva, T.; Muller, S.; Gartner, S.; Sures, I.; Wang,H.; Imyanitov, E.; Haring, H.-U.; Knayzev, P.; Iacobelli, S.; Hofler,H.; Ullrich, A.: Cancer progression and tumor cell motility are associatedwith the FGFR4 Arg388 allele. Cancer Res. 62: 840-847, 2002.

[0600] 198.Holtrich, U.; Brauninger, A.; Strebhardt, K.; Rubsamen-Waigmann,H.: Two additional protein-tyrosine kinases expressed in human lung:fourth member of the fibroblast growth factor receptor family andan intracellular protein-tyrosine kinase. Proc. Nat. Acad. Sci. 88:10411-10415, 1991.

[0601] 199.Kostrzewa, M.; Muller, U.: Genomic structure and complete sequenceof the human FGFR4 gene. Mammalian Genome 9: 131-135, 1998.

[0602] 200.Partanen, J.; Makela, T. P.; Eerola, E.; Korhonen, J.; Hirvonen,H.; Claesson-Welsh, L.; Alitalo, K.: FGFR-4, a novel acidic fibroblastgrowth factor receptor with a dis-

tinct expression pattern. EMBO J. 10:1347–1354, 1991.

[0603] 201.Scott, A. F.: Personal Communication. Baltimore, Md. 10/12/1999.

[0604] 202.Vainikka, S.; Partanen, J.; Bellosta, P.; Coulier, F.; Basilico,C.; Jaye, M.; Alitalo, K.: Fibroblast growth factor receptor-4 showsnovel features in genomic structure, ligand binding and signal transduction. EMBOJ. 11: 4273–4280, 1992.

[0605] 203.Warrington, J. A.; Bailey, S. K.; Armstrong, E.; Aprelikova, O.;Alitalo, K.; Dolganov, G. M.; Wilcox, A. S.; Sikela, J. M.; Wolfe,S. F.; Lovett, M.; Wasmuth, J. J.: A radiation hybrid map of 18 growthfactor, growth factor receptor, hormone receptor, or neurotransmitterreceptor genes on the distal region of the long arm of chromosome5. Genomics 13: 803–808, 1992.

[0606] 204.Diaz, M. O.; Bohlander, S.: Nomenclature of the human interferongenes. J. Interferon Res. 13: 443–444, 1993.

[0607] 205.Olopade, O. I.; Bohlander, S. K.; Pomykala, H.; Maltepe, E.; VanMelle, E.; Le Beau, M. M.; Diaz, M. O.: Mapping of the shortest regionof overlap of deletions of the short arm of chromosome 9 associatedwith human neoplasia. Genomics 14: 437–443, 1992.

[0608] 206.Habas, R.; Kato, Y.; He, X.: Wnt/Frizzled activation of Rho regulatesvertebrate gastrulation and requires a novel Formin homology proteinDaam1. Cell 107: 843–854, 2001.

[0609] 207.Tollervey, D.; Kiss, T.: Function and synthesis of small nucleolarRNAs. Curr. Opin. Cell Biol. 9: 337–342, 1997.

[0610] 208.Pogacic, V.; Dragon, F.; Filipowicz, W.: Human H/ACA small nucleolarRNPs and telomerase share evolutionarily conserved proteins NHP2 andNOP10. Molec. Cell. Biol. 20: 9028–9040, 2000.

[0611] 209.Olavesen, M. G.; Bentley, E.; Mason, R. V. F.; Stephens, R. J.;Ragoussis, J.: Fine mapping of 39 ESTs on human chromosome 6p23–p25. Genomics 46:303–306, 1997.

[0612] 210.Blake, D. J.; Love, D. R.; Tinsley, J.; Morris, G. E.; Tur- ley,H.; Gatter, K.; Dickson, G.; Edwards, Y. H.; Davies, K. E.: Characterizationof a 4.8kb transcript from the Duchenne muscular dystrophy locus expressedin schwan- noma cells. Hum. Molec. Genet. 1: 103–109, 1992.

[0613] 211.Fuentes, J. J.; Genesca, L.; Kingsbury, T. J.; Cunning- ham, K. W.;Perez–Riba, M.; Estivill, X.; de la Luna, S.: DSCR1, overexpressedin Down syndrome, is an inhibitor of calcineurin–mediated signalingpathways. Hum. Molec.

Genet. 9: 1681–1690, 2000.

[0614] 212.Nagase, T.; Ishikawa, K.; Suyama, M.; Kikuno, R.; Hirosawa, M.;Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O.: Predictionof the coding sequences of unidentified human genes. XII. The completesequences of 100 new cDNA clones from brain which code for large proteinsin vitro. DNA Res. 5: 355–364, 1998.

[0615] 213.Belinsky, M. G.; Bain, L. J.; Balsara, B. B.; Testa, J. R.; Kruh,G. D.: Characterization of MOAT–C and MOAT–D, new members of theMRP/cMOAT subfamily of transporter proteins. J. Nat. Cancer Inst. 90:1735–1741, 1998.

[0616] 214.Fromm, M. F.; Leake, B.; Roden, D. M.; Wilkinson, G. R.; Kim, R.B.: Human MRP3 transporter: identification of the 5–prime flankingregion, genomic organization and alternative splice variants. Biochim.Biophys. Acta 1415: 369–374, 1999.

[0617] 215.Kiuchi, Y.; Suzuki, H.; Hirohashi, T.; Tyson, C. A.; Sugiyama,Y.: cDNA cloning and inducible expression of human multidrug resistanceassociated protein 3 (MRP3). FEBS Lett. 433: 149–152, 1998.

[0618] 216.Konig, J.; Rost, D.; Cui, Y.; Keppler, D.: Characterization ofthe human multidrug resistance protein isoform MRP3 localized to thebasolateral hepatocyte membrane.

Hepatology 29: 1156–1163, 1999.

[0619] 217.Kool, M.; van der Linden, M.; de Haas, M.; Scheffer, G. L.; deVree, J. M. L.; Smith, A. J.; Jansen, G.; Peters, G. J.; Ponne, N.;Scheper, R. J.; Oude Elferink, R. P. J.; Baas, F.; Borst, P.: MRP3,an organic anion transporter able to transport anti-cancer drugs. Proc.Nat. Acad. Sci. 96: 6914–6919, 1999.

[0620] 218.Ortiz, D. F.; Li, S.; Iyer, R.; Zhang, X.; Novikoff, P.; Arias,I. M.: MRP3, a new ATP-binding cassette protein localized to thecanalicular domain of the hepatocyte. Am. J. Physiol. 276: G1493–G1500,1999.

[0621] 219.Santoro, M.; Carlomagno, F.; Hay, I. D.; Herrmann, M. A.; Grieco,M.; Melillo, R.; Pierotti, M. A.; Bongarzone, I.; Della Porta, G.;Berger, N.; Peix, J. L.; Paulin, C.; Fabien, N.; Vecchio, G.; Jenkins,R. B.; Fusco, A.: Ret oncogene activation in human thyroid neoplasmsis restricted to the papillary cancer subtype. J. Clin. Invest. 89:1517–1522, 1992.

[0622] 220.Santoro, M.; Carlomagno, F.; Romano, A.; Bottaro, D. P.; Dathan,N. A.; Grieco, M.; Fusco, A.; Vecchio, G.; Matoskova, B.; Kraus, M.H.; Di Fiore, P. P.: Activation of RET as a dominant transforminggene by germline mutations of MEN2A and MEN2B. Science 267: 381–383,1995.

[0623] 221.Schuchardt, A.; D'Agati, V.; Larsson-Blomberg, L.;

Costantini,F.; Pachnis, V.: Defects in the kidney and enteric nervous systemof mice lacking the tyrosine kinase receptor Ret. Nature 367: 380-383,1994.

[0624] 222.Shirahama, S.; Ogura, K.; Takami, H.; Ito, K.; Tohsen, T.; Miyauchi,A.; Nakamura, Y.: Mutational analysis of the RET proto-oncogene in71 Japanese patients with medullary thyroid carcinoma. J. Hum. Genet. 43:101-106, 1998.

[0625] 223.Seri, M.; Yin, L.; Barone, A.; Bolino, A.; Celli, I.; Bocciardi,R.; Pasini, B.; Ceccherini, I.; Lerone, M.; Kristoffersson, U.; Larsson,L. T.; Casasa, J. M.; Cass, D. T.; Abramowicz, M. J.; Vanderwinden,J.-M.; Kravcenkiene, I.; Baric, I.; Silengo, M.; Martucciello, G.;Romeo, G.: Frequency of RET mutations in long- and short-segmentHirschsprung disease. Hum. Mutat. 9: 243-249, 1997.

[0626] 224.Takahashi, M.; Buma, Y.; Hiai, H.: Isolation of ret proto-oncogenecDNA with an amino-terminal signal sequence. Oncogene 4: 805-806,1989.

[0627] 225.Takahashi, M.; Buma, Y.; Iwamoto, T.; Inaguma, Y.; Ikeda, H.;Hiai, H.: Cloning and expression of the ret proto-oncogene encodinga tyrosine kinase with two potential transmembrane domains. Oncogene 3:571-578,

1988.

[0628] 226.Takahashi, M.; Ritz, J.; Cooper, G. M.: Activation of a novelhuman transforming gene, ret, by DNA rearrangement. Cell 42: 581-588,1985.

[0629] 227.Tessitore, A.; Sinisi, A. A.; Pasquali, D.; Cardone, M.; Vitale,D.; Bellastella, A.; Colantuoni, V.: A novel case of multiple endocrineneoplasia type 2A associated with two de novo mutations of the RETprotooncogene. J. Clin. Endocr. Metab. 84: 3522-3527, 1999.

[0630] 228.van Heyningen, V.: One gene--four syndromes. Nature 367: 319-320,1994.

[0631] 229.Xue, F.; Yu, H.; Maurer, L. H.; Memoli, V. A.; Nutile-McMenemey,N.; Schuster, M. K.; Bowden, D. W.; Mao, J.; Noll, W. W.: GermlineRET mutations in MEN 2A and FMTC and their detection by simple DNAdiagnostic tests. Hum. Molec. Genet. 3: 635-638, 1994.

[0632] 230.Yin, L.; Ceccherini, I.; Pasini, B.; Matera, I.; Bicocchi, M.P.; Barone, V.; Bocciardi, R.; Kaariainen, H.; Weber, D.; Devoto,M.; Romeo, G.: Close linkage with the RET protooncogene and boundariesof deletion mutations in autosomal dominant Hirschsprung disease. Hum.Molec. Genet. 2: 1803-1808, 1993.

[0633] 231.Schuuring, E.; Verhoeven, E.; Mooi, W. J.; Michalides,

R. J. A.M.: Identification and cloning of two overexpressed genes, U21B31/PRAD1and EMS1, within the amplified chromosome 11q13 region in human carcinomas. Onco-gene 7:355-361, 1992.

[0634] 232.van Damme, H.; Brok, H.; Schuuring-Scholtes, E.; Schuuring, E.: The redistribution of cortactin into cell-matrix contact sites inhuman carcinoma cells with 11q13 amplification is associated withboth overexpression and post-translational modification. J. Biol.Chem. 272: 7374-7380, 1997.

[0635] 233.Yamashita, A.; Ohnishi, T.; Kashima, I.; Taya, Y.; Ohno, S.: HumanSMG-1, a novel phosphatidylinositol 3-kinase-related protein kinase,associates with components of the mRNA surveillance complex and isinvolved in the regulation of nonsense-mediated mRNA decay. GenesDev. 15: 2215-2228, 2001.

[0636] 234.Nagle, D. L.; McGrail, S. H.; Vitale, J.; Woolf, E. A.; Dussault,B. J., Jr.; DiRocco, L.; Holmgren, L.; Montagno, J.; Bork, P.; Huszar,D.; Fairchild-Huntress, V.; Ge, P.; Keilty, J.; Ebelling, C.; Baldini,L.; Gilchrist, J.; Burr, P.; Carlson, G. A.; Moore, K. J.: The mahoganyprotein is a receptor in-volved in suppression of obesity. Nature 398:148-151, 1999.

[0637] 235.Brown, C. W.; Houston-Hawkins, D. E.; Woodruff, T. K.; Matzuk,M. M.: Insertion of Inhbb into the Inhba locus rescues the Inhba-nullphenotype and reveals new activin functions. Nature Genet. 25: 453-457,2000.

[0638] 236.Ferguson, C. A.; Tucker, A. S.; Christensen, L.; Lau, A. L.; Matzuk,M. M.; Sharpe, P. T.: Activin is an essential early mesenchymal signalin tooth development that is required for patterning of the murinedentition. Genes Dev. 12: 2636-2649, 1998.

[0639] 237.Burger, H. G.; Igarashi, M.; Baird, D.; Mason, T.; Bardin, W.;McLachlan, R.; Chappel, S.; Miyamoto, K.; de Jong, F.; Moudgal, A.;Demoulin, A.; Nieschlag, E.; de Kretser, D.; Robertson, D.; Findlay,J.; Sasamoto, S.; Forage, R.; Schwartz, N.; Fukuda, M.; Steinberger,A.; Hasegawa, Y.; Tanabe, K.; Ling, N.; Ying, S.-Y.: Inhibin: definitionand nomenclature, including related substances. (Letter) J. Clin.Endocr. Metab. 66: 885-886, 1988.

[0640] 238.Lumpkin, M. D.; Moltz, J. H.; Yu, W. H.; Samson, W. K.; McCann,S. M.: Purification of FSH-releasing factor: its dis-similarity fromLHRH of mammalian, avian, and piscian ori-gin. Brain Res. Bull. 18:175-178, 1987.

[0641] 239.Matzuk, M. M.; Kumar, T. R.; Vassalli, A.; Bickenbach, J. R.; Roop,D. R.; Jaenisch, R.; Bradley, A.: Functional anal-

ysis of activinsduring mammalian development. Nature 374: 354-356, 1995.

[0642] 240.Mellor, S. L.; Cranfield, M.; Ries, R.; Pedersen, J.; Can-cilla,B.; de Kretser, D.; Groome, N. P.; Mason, A. J.; Ris-bridger, G. P.: Localization of activin beta(A)-, beta(B)-, and beta(C)-subunitsin human prostate and evidence for formation of new activin heterodimersof beta(C)-subunit. J. Clin. Endocr. Metab. 85: 4851-4858, 2000.

[0643] 241.Murata, M.; Eto, Y.; Shibai, H.; Sakai, M.; Muramatsu, M.: Erythroiddifferentiation factor is encoded by the same mRNA as that of theinhibin beta-A chain. Proc. Nat. Acad. Sci. 85: 2434-2438, 1988.

[0644] 242.You, L.; Kruse, F. E.: Differential effect of activin A and BMP-7on myofibroblast differentiation and the role of the Smad signalingpathway. Invest. Ophthal. Vis. Sci. 43: 72-81, 2002.

[0645] 243.El-Husseini, A. E.-D.; Schnell, E.; Chetkovich, D. M.; Nicoll,R. A.; Bredt, D. S.: PSD-95 involvement in matura-tion of excitatorysynapses. Science 290: 1364-1368, 2000.

[0646] 244.El-Husseini, A. E.-D.; Schnell, E.; Dakoji, S.; Sweeney, N.; Zhou,Q.; Prange, O.; Gauthier-Campbell, C.; Aguilera-Moreno, A.; Nicoll,R. A.; Bredt, D. S.: Synaptic strength

regulated by palmitate cyclingon PSD-95. Cell 108: 849-863, 2002.

[0647] 245.Kim, E.; Cho, K.-O.; Rothschild, A.; Sheng, M.: Heteromultimerizationand NMDA receptor-clustering activity of Chapsyn-110, a member ofthe PSD-95 family of proteins. Neuron 17: 103-113, 1996.

[0648] 246.Kim, E.; Niethammer, M.; Rothschild, A.; Jan, Y. N.; Sheng, M.: Clustering of Shaker-type K+ channels by interaction with a familyof membrane-associated guanylate kinases. Nature 378: 85-88, 1995.

[0649] 247.Kistner, U.; Wenzel, B. M.; Veh, R. W.; Cases-Langhoff, C.; Garner,A. M.; Appeltauer, U.; Voss, B.; Gundelfinger, E. D.; Garner, C. C.: SAP90, a rat presynaptic protein related to the product of the Drosophilatumor suppressor gene, dLg-A. J. Biol. Chem. 268: 4580-4583, 1993.

[0650] 248.Migaud, M.; Charlesworth, P.; Dempster, M.; Webster, L. C.; Watabe,A. M.; Makhinson, M.; He, Y.; Ramsay, M. F.; Morris, R. G. M.; Morrison,J. H.; O'Dell, T. J.; Grant, S. G. N.: Enhanced long-term potentiationand impaired learning in mice with mutant postsynaptic density-95protein. Nature 396: 433-439, 1998.

[0651] 249.Sattler, R.; Xiong, Z.; Lu, W.-Y.; Hafner, M.; MacDon-

ald, J. F.;Tymianski, M.: Specific coupling of NMDA recep-tor activation to nitricoxide neurotoxicity by PSD-95 pro-tein. Science 284: 1845-1848, 1999.

[0652] 250.Stathakis, D. G.; Hoover, K. B.; You, Z.; Bryant, P. J.: Humanpostsynaptic density-95 (PSD95): location of the gene (DLG4) and possiblefunction in nonneural as well as in neural tissues. Genomics 44:71-82, 1997.

[0653] 251.Strippoli, P.; Petrini, M.; Lenzi, L.; Carinci, P.; Zannotti, M.: The murine DSCR1-like (Down syndrome candidate region 1) gene family:conserved synteny with the human orthologous genes. Gene 257: 223-232,2000.

[0654] 252.Yang, J.; Rothermel, B.; Vega, R. B.; Frey, N.; McKin-sey, T. A.;Olson, E. N.; Bassel-Duby, R.; Williams, R. S.: In-dependent signalscontrol expression of the calcineurin in-hibitory proteins MCIP1 andMCIP2 in striated muscles. Circ. Res. 87: 61e-68e, 2000.

[0655] 253.Denning, G.; Jamieson, L.; Maquat, L. E.; Thompson, E. A.; Fields,A. P.: Cloning of a novel phosphatidylinositol kinase-related kinase:characterization of the human SMG-1 RNA surveillance protein. J.Biol. Chem. 276: 22709-22714, 2001.

[0656] 254.Diaz-Meco, M. T.; Municio, M. M.; Sanchez, P.; Lozano, J.; Moscat,J.: Lambda-interacting protein, a novel

protein that specificallyinteracts with the zinc finger domain of the atypical protein kinaseC isotype lambda/iota and stimulates its kinase activity in vitroand in vivo. Molec. Cell. Biol. 16: 105-114, 1996.

[0657] 255.Alarcon, B.; Regueiro, J. R.; Arnaiz-Villena, A.; Terhorst, C.: Familial defect in the surface expression of the T-cell receptor-CD3complex. New Eng. J. Med. 319: 1203-1208, 1988.

[0658] 256.Caplan, S.; Zeliger, S.; Wang, L.; Baniyash, M.: Cell-surface-expressedT-cell antigen-receptor epsilon chain is associated with the cytoskeleton. Proc.Nat. Acad. Sci. 92: 4768-4772, 1995.

[0659] 257.Clevers, H.; Alarcon, B.; Wileman, T.; Terhorst, C.: The T cellreceptor/CD3 complex: a dynamic protein ensemble. Annu. Rev. Immun. 6:629-662, 1988.

[0660] 258.Grakoui, A.; Bromley, S. K.; Sumen, C.; Davis, M. M.; Shaw, A.S.; Allen, P. M.; Dustin, M. L.: The immunological synapse: a molecularmachine controlling T cell activation. Science 285: 221-227, 1999.

[0661] 259.Krummel, M. F.; Sjaastad, M. D.; Wulfing, C.; Davis, M. M.: Differentialclustering of CD4 and CD3-zeta during T cell recognition. Science 289:1349-1352, 2000.

[0662] 260.Weissman, A. M.; Baniyash, M.; Hou, D.; Samelson, L.

E.; Burgess,W. H.; Klausner, R. D.: Molecular cloning of the zeta chain of theT cell antigen receptor. Science 239: 1018-1021, 1988.

[0663] 261.Weissman, A. M.; Hou, D.; Orloff, D. G.; Modi, W. S.; Seuanez,H.; O'Brien, S. J.; Klausner, R. D.: Molecular cloning and chromosomallocalization of the human T-cell receptor zeta chain: distinctionfrom the molecular CD3 complex. Proc. Nat. Acad. Sci. 85: 9709-9713,1988.

[0664] 262.Weissman, A. M.; Samelson, L. E.; Klausner, R. D.: A new subunitof the human T-cell antigen receptor com- plex. Nature 324: 480-482,1986.

[0665] 263.Patel, A.; Rochelle, J. M.; Jones, J. M.; Sumegi, J.; Uhl, G. R.;Seldin, M. F.; Meisler, M. H.; Gregor, P.: Mapping of the taurinetransporter gene to mouse chromosome 6 and to the short arm of humanchromosome 3. Genomics 25: 314-317, 1995.

[0666] 264.Ramamoorthy, S.; Leibach, F. H.; Mahesh, V. B.; Han, H.; Yang-Feng,T.; Blakely, R. D.; Ganapathy, V.: Functional characterization andchromosomal localization of a cloned taurine transporter from humanplacenta. Biochem. J. 300: 893-900, 1994.

[0667] 265.Uchida, S.; Kwon, H. M.; Yamauchi, A.; Preston, A. S.; Marumo,F.; Handler, J. S.: Molecular cloning of the cDNA

for an MDCK cellNa(+)- and Cl(-)-dependent taurine transporter that is regulated byhypertonicity. Proc. Nat. Acad. Sci. 89: 8230-8234, 1992.

[0668] 266.Durand, B.; Sperisen, P.; Emery, P.; Barras, E.; Zufferey, M.;Mach, B.; Reith, W.: RFXAP, a novel subunit of the RFX DNA bindingcomplex is mutated in MHC class II deficiency. EMBO J. 16: 1045-1055,1997.

[0669] 267.Nekrep, N.; Jabrane-Ferrat, N.; Peterlin, B. M.: Mutations inthe bare lymphocyte syndrome define critical steps in the assemblyof the regulatory factor X complex. Molec. Cell Biol. 20: 4455-4461,2000.

[0670] 268.Peijnenburg, A.; Van Eggermond, M. C. J. A.; Van den Berg, R.;Sanal, O.; Vossen, J. M. J. J.; Van den Elsen, P. J.: Molecular analysisof an MHC class II deficiency patient reveals a novel mutation inthe RFX5 gene. Immunogenetics 49: 338-345, 1999.

[0671] 269.Fuentes, J.-J.; Pritchard, M. A.; Planas, A. M.; Bosch, A.; Ferrer,I.; Estivill, X.: A new human gene from the Down syndrome criticalregion encodes a proline-rich protein highly expressed in fetal brainand heart. Hum. Molec. Genet. 4: 1935-1944, 1995.

[0672] 270.Wolf, H. M.; Hauber, I.; Gulle, H.; Thon, V.; Eggenbauer, H.;Fischer, M. B.; Fiala, S.; Eibl, M. M.: Brief report:

Twin boys withmajor histocompatibility complex class II deficiency but inducibleimmune responses. New Eng. J. Med. 332: 86-90, 1995.

[0673] 271.Doi, A.; Shiosaka, T.; Takaoka, Y.; Yanagisawa, K.; Fujita, S.: Molecular cloning of the cDNA encoding A+U-rich element RNA bindingfactor. Biochim. Biophys. Acta 1396: 51-56, 1998.

[0674] 272.Kamei, D.; Tsuchiya, N.; Yamazaki, M.; Meguro, H.; Yamada, M.:Two forms of expression and genomic structure of the human heterogeneousnuclear ribonucleoprotein D-like JKTBP gene (HNRPDL). Gene 228:13-22, 1999.

[0675] 273.Tsuchiya, N.; Kamei, D.; Takano, A.; Matsui, T.; Yamada, M.: Cloningand characterization of a cDNA encoding a novel heterogeneous nuclearribonucleoprotein-like protein and its expression in myeloid leukemiacells. J. Biochem. 123: 499-507, 1998.

[0676] 274.Fuentes, J. J.; Pritchard, M. A.; Estivill, X.: Genomic organization,alternative splicing, and expression patterns of the DSCR1 (Down syndromecandidate region 1) gene. Genomics 44: 358-361, 1997.

[0677] 275.Kingsbury, T. J.; Cunningham, K. W.: A conserved family of calcineurinregulators. Genes Dev. 14: 1595-1604, 2000.

[0678] 276.Rothermel, B.; Vega, R. B.; Yang, J.; Wu, H.; Bassel-Duby, R.;Williams, R. S.: A protein encoded within the Down syndrome criticalregion is enriched in striated muscles and inhibits calcineurin signaling. J.Biol. Chem. 275: 8719-8725, 2000.

[0679] 277.Steimle, V.; Durand, B.; Barras, E.; Zuffrey, M.; Hadam, M. R.;Mach, B.; Reith, W.: A novel DNA binding regulatory factor is mutatedin primary MHC class II deficiency (bare lymphocyte syndrome). GenesDev. 9: 1021-1032, 1995.

[0680] 278.Villard, J.; Reith, W.; Barras, E.; Gos, A.; Morris, M. A.; Antonarakis,S. E.; Van den Elsen, P. J.; Mach, B.: Analysis of mutations andchromosomal localisation of the gene encoding RFX5, a novel transcriptionfactor affected in major histocompatibility complex class II deficiency. Hum.Mutat. 10: 430-435, 1997.

[0681] 279.Scott, A. F.: Personal Communication. Baltimore, Md. 7/20/2001.

[0682] 280.Arsenijevic, D.; Onuma, H.; Pecqueur, C.; Raimbault, S.; Manning,B. S.; Miroux, B.; Couplan, E.; Alves-Guerra, M.-C.; Goubern, M.;Surwit, R.; Bouillard, F.; Richard, D.; Collins, S.; Ricquier, D.: Disruption of the uncoupling protein-2 gene in mice reveals a rolein immunity and reactive oxygen species production. Nature Genet. 26:435-439,

2000.

[0683] 281.Bouchard, C.; Perusse, L.; Chagnon, Y. C.; Warden, C.; Ricquier,D.: Linkage between markers in the vicinity of the uncoupling protein2 gene and resting metabolic rate in humans. Hum. Molec. Genet. 6:1887-1889, 1997.

[0684] 282.Brauner, P.; Nibbelink, M.; Flachs, P.; Vitkova, I.; Kopecky, P.;Mertelikova, I.; Janderova, L.; Penicaud, L.; Casteilla, L.; Plavka,R.; Kopecky, J.: Fast decline of hematopoiesis and uncoupling protein2 content in human liver after birth: location of the protein in Kupffercells. Pediat. Res. 49: 440-447, 2001.

[0685] 283.Esterbauer, H.; Schneitler, C.; Oberkofler, H.; Eben-bichler, C.;Paulweber, B.; Sandhofer, F.; Ladurner, G.; Hell, E.; Strosberg, A.D.; Patsch, J. R.; Krempler, F.; Patsch, W.: A common polymorphismin the promoter of UCP2 is associated with decreased risk of obesityin middle-aged humans. Nature Genet. 28: 178-183, 2001.

[0686] 284.Fleury, C.; Neverova, M.; Collins, S.; Raimbault, S.; Champigny,O.; Levi-Meyrueis, C.; Bouillaud, F.; Seldin, M. F.; Surwit, R. S.;Ricquier, D.; Warden, C. H.: Uncoupling protein-2: a novel gene linkedto obesity and hyperinsulinemia. Nature Genet. 15: 269-272, 1997.

[0687] 285.Flier, J. S.; Lowell, B. B.: Obesity research springs a

protonleak. Nature Genet. 15: 223-224, 1997.

[0688] 286.Millet, L.; Vidal, H.; Andreelli, F.; Larrouy, D.; Riou, J.-P.;Ricquier, D.; Laville, M.; Langin, D.: Increased uncoupling protein-2and -3 mRNA expression during fasting in obese and lean humans. J.Clin. Invest. 100: 2665-2670, 1997.

[0689] 287.Suetsugu, S.; Miki, H.; Takenawa, T.: Identification of two humanWAVE/SCAR homologues as general actin regulatory molecules which associatewith the Arp2/3 complex. Biochem. Biophys. Res. Commun. 260: 296-302,1999.

[0690] 288.Wang, A. H.; Bertos, N. R.; Vezmar, M.; Pelletier, N.; Crosato,M.; Heng, H. H.; Th'ng, J.; Han, J.; Yang, X.-J.: HDAC4, a humanhistone deacetylase related to yeast HDA1, is a transcriptional corepressor. Molec.Cell. Biol. 19: 7816-7827, 1999.

[0691] 289.Hirsch, D. S.; Pirone, D. M.; Burbelo, P. D.: A new family ofCdc42 effector proteins, CEPs, function in fibroblast and epithelialcell shape changes. J. Biol. Chem. 276: 875-883, 2001.

[0692] 290.Joberty, G.; Perlungher, R. R.; Macara, I. G.: The Borgs, a newfamily of Cdc42 and TC10 GTPase-interacting proteins. Molec. Cell.Biol. 19: 6585-6597, 1999.

[0693] 291.McCright, B.; Brothman, A. R.; Virshup, D. M.: Assignment of humanprotein phosphatase 2A regulatory subunit genes B56-alpha, B56-beta,B56-gamma, B56-delta, and B56-epsilon (PPP2R5A--PPP2R5E), highly expressedin muscle and brain, to chromosome regions 1q41, 11q12, 3p21, 6p21.1,and 7p11.2-to-p12. Genomics 36: 168-170, 1996.

[0694] 292.McCright, B.; Virshup, D. M.: Identification of a new family ofprotein phosphatase 2A regulatory subunits. J. Biol. Chem. 270:26123-26128, 1995.

[0695] 293.Zhang, C.-Y.; Baffy, G.; Perret, P.; Krauss, S.; Peroni, O.; Grujic,D.; Hagen, T.; Vidal-Puig, A.; Boss, O.; Kim, Y.-B.; Zheng, X. X.;Wheeler, M. B.; Shulman, G. I.; Chan, C. B.; Lowell, B. B.: Uncouplingprotein-2 negatively regulates insulin secretion and is a major linkbetween obesity, beta cell dysfunction, and type 2 diabetes. Cell 105:745-755, 2001.

[0696] 294.Park, W. S.; Lee, J. H.; Shin, M. S.; Park, J. Y.; Kim, H. S.;Lee, J. H.; Kim, Y. S.; Lee, S. N.; Xiao, W.; Park, C. H.; Lee, S.H.; Yoo, N. J.; Lee, J. Y.: Inactivating mutations of the caspase-10gene in gastric cancer. Oncogene 21: 2919-2925, 2002.

[0697] 295.Shin, M. S.; Kim, H. S.; Kang, C. S.; Park, W. S.; Kim, S.

Y.;Lee, S. N.; Lee, J. H.; Park, J. Y.; Jang, J. J.; Kim, C. W.; Kim,S. H.; Lee, J. Y.; Yoo, N. J.; Lee, S. H.: Inactivating mutationsof CASP10 gene in non-Hodgkin lymphomas. Blood 99: 4094-4099, 2002.

[0698] 296.Vincenz, C.; Dixit, V. M.: Fas-associated death domain proteininterleukin-1-beta-converting enzyme 2 (FLICE2), an ICE/Ced-3 homologue,is proximally involved in CD95- and p55-mediated death signaling. J.Biol. Chem. 272: 6578-6583, 1997.

[0699] 297.Wang, J.; Chun, H. J.; Wong, W.; Spencer, D. M.; Lenardo, M. J.: Caspase-10 is an initiator caspase in death receptor signaling. Proc.Nat. Acad. Sci. 98: 13884-13888, 2001.

[0700] 298.Wang, J.; Zheng, L.; Lobito, A.; Chan, F. K.; Dale, J.; Sneller,M.; Yao, X.; Puck, J. M.; Straus, S. E.; Lenardo, M. J.: Inheritedhuman caspase 10 mutations underlie defective lymphocyte and dendriticcell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell 98:47-58, 1999.

[0701] 299.Nagase, T.; Ishikawa, K.; Miyajima, N.; Tanaka, A.; Kotani, H.;Nomura, N.; Ohara, O.: Prediction of the coding sequences of unidentifiedhuman genes. IX. The complete sequences of 100 new cDNA clones frombrain which can

code for large proteins in vitro. DNA Res. 5: 31–39,1998.

[0702]   300.den Dunnen, J. T.; Grootscholten, P. M.; Bakker, E.;

Blonden,L. A. J.; Ginjaar, H. B.; Wapenaar, M. C.; van

Paassen, H. M. B.;van Broeckhoven, C.; Pearson, P. L.; van

Ommen, G. J. B.: Topographyof the Duchenne muscular

dystrophy (DMD) gene: FIGE and cDNA analysisof 194

cases reveals 115 deletions and 13 duplications. Am. J.

Hum.Genet. 45: 835–847, 1989.

[0703]   301.Vanhalst, K.; Kools, P.; Eynde, E. V.; van Roy, F.: The

humanand murine protocadherin–beta one–exon gene

families show high evolutionaryconservation, despite the

difference in gene number. FEBS Lett. 495:120–125, 2001.

[0704]   302.Goldowitz, D.; Smeyne, R. J.: Tune into the weaver

channel. NatureGenet. 11: 107–109, 1995.

[0705]   303.Hess, E. J.: Identification of the weaver mouse muta-

tion: theend of the beginning. Neuron 16: 1073–1076,

1996.

[0706]   304.Lane, P. W.: New mutation: Weaver, wv. Mouse News

Letter 32–33,1964.

[0707]   305.Lesage, F.; Duprat, F.; Fink, M.; Guillemare, E.; Cop-

pola, T.;Lazdunski, M.; Hugnot, J.–P.: Cloning provides ev-

idence for a familyof inward rectifier and G–protein cou-

pled K(+) channels in the brain. FEBSLett. 353: 37–42,

1994.

[0708] 306.Rakic, P.; Sidman, R. L.: Sequence of developmental abnormalitiesleading to granule cell deficit in cerebellar cortex of weaver mutantmice. J. Comp. Neurol. 152: 103-132, 1973.

[0709] 307.Sakura, H.; Bond, C.; Warren-Perry, M.; Horsley, S.; Kearney, L.;Tucker, S.; Adelman, J.; Turner, R.; Ashcroft, F. M.: Characterizationand variation of a human inwardly-rectifying K-channel gene (KCNJ6):a putative ATP-sensitive K-channel subunit. FEBS Lett. 367: 193-197,1995.

[0710] 308.Tsaur, M.-L.; Menzel, S.; Lai, F.-P.; Espinosa, R., III; Concannon,P.; Spielman, R. S.; Hanis, C. L.; Cox, N. J.; Le Beau, M. M.; German,M. S.; Jan, L. Y.; Bell, G. I.; Stoffel, M.: Isolation of a cDNAclone encoding a K(ATP) channel-like protein expressed in insulin-secretingcells, localization of the human gene to chromosome band 21q22.1 andlinkage studies with NIDDM. Diabetes 44: 592-596, 1995.

[0711] 309.Yasuda, K.; Sakura, H.; Mori, Y.; Iwamoto, K.; Shimokawa, K.;Kadowaki, H.; Hagura, R.; Akanuma, Y.; Adelman, J. P.; Yazaki, Y.;Ashcroft, F. M.; Kadowaki, T.: No evidence for mutations in a putativesubunit of the beta-cell ATP-sensitive potassium channel (K-ATP channel)in

Japanese NIDDM patients. Biochem. Biophys. Res. Commun. 211:1036-1040, 1995.

[0712] 310.Gospe, S. M., Jr.; Lazaro, R. P.; Lava, N. S.; Grootscholten,P. M.; Scott, M. O.; Fischbeck, K. H.: Familial X-linked myalgiaand cramps: a nonprogressive myopathy associated with a deletion inthe dystrophin gene. Neurology 39: 1277-1280, 1989.

[0713] 311.Kingston, H. M.; Sarfarazi, M.; Thomas, N. S. T.; Harper, P. S.: Localisation of the Becker muscular dystrophy gene on the shortarm of the X chromosome by linkage to cloned DNA sequences. Hum.Genet. 67: 6-17, 1984.

[0714] 312.Kingston, H. M.; Thomas, N. S. T.; Pearson, P. L.; Sarfarazi,M.; Harper, P. S.: Genetic linkage between Becker muscular dystrophyand a polymorphic DNA sequence on the short arm of the X chromosome. J.Med. Genet. 20: 255-258, 1983.

[0715] 313.Acampora, D.; Postiglione, M. P.; Avantaggiato, V.; Di Bonito,M.; Vaccarino, F. M.; Michaud, J.; Simeone, A.: Progressive impairmentof developing neuroendocrine cell lineages in the hypothalamus ofmice lacking the Orthopedia gene. Genes Dev. 13: 2787-2800, 1999.

[0716] 314.Lin, X.; State, M. W.; Vaccarino, F. M.; Greally, J.; Hass,

M.;Leckman, J. F.: Identification, chromosomal assign-ment, and expressionanalysis of the human home-odomain-containing gene Orthopedia (OTP). Genomics 60:96–104, 1999.

[0717] 315.Fernandes-Alnemri, T.; Armstrong, R. C.; Krebs, J.; Srinivasula,S. M.; Wang, L.; Bullrich, F.; Fritz, L. C.; Tra-pani, J. A.; Tomaselli,K. J.; Litwack, G.; Alnemri, E. S.: In vitro activation of CPP32and Mch3 by Mch4, a novel hu-man apoptotic cysteine protease containingtwo FADD-like domains. Proc. Nat. Acad. Sci. 93: 7464–7469, 1996.

[0718] 316.Fernandes-Alnemri, T.; Litwack, G.; Alnemri, E. S.: CPP32, a novelhuman apoptotic protein with homology to Caenorhabditis elegans celldeath protein Ced-3 and mammalian interleukin-1 beta-converting enzyme. J.Biol. Chem. 269: 30761–30764, 1994.

[0719] 317.Fernando, P.; Kelly, J. F.; Balazsi, K.; Slack, R. S.; Megeney,L. A.: Caspase 3 activity is required for skeletal muscle differentiation. Proc.Nat. Acad. Sci. 99: 11025–11030, 2002.

[0720] 318.Huang, Y.; Shin, N.-H.; Sun, Y.; Wang, K. K. W.: Molecular cloningand characterization of a novel caspase-3 variant that attenuatesapoptosis induced by proteasome inhibition. Biochem. Biophys. Res.Commun. 283:

762-769, 2001.

[0721] 319.Kuida, K.; Zheng, T. S.; Na, S.; Kuan, C.; Yang, D.; Karasuyama,H.; Rakio, P.; Flavell, R. A.: Decreased apoptosis in the brain andpremature lethality in CPP32-deficient mice. Nature 384: 368-372,1996.

[0722] 320.Levkau, B.; Koyama, H.; Raines, E. W.; Clurman, B. E.; Herren,B.; Orth, K.; Roberts, J. M.; Ross, R.: Cleavage of p21(Cip1/Waf1)and p27(Kip1) mediates apoptosis in endothelial cells through activationof Cdk2: role of a caspase cascade. Molec. Cell 1: 553-563, 1998.

[0723] 321.Nasir, J.; Theilmann, J. L.; Chopra, V.; Jones, A. M.; Walker,D.; Rasper, D. M.; Vaillancourt, J. P.; Hewitt, J. E.; Nicholson,D. W.; Hayden, M. R.: Localization of the cell death genes CPP32and Mch-2 to human chromosome 4q. Mammalian Genome 8: 56-59, 1997.

[0724] 322.Tiso, N.; Pallavicini, A.; Muraro, T.; Zimbello, R.; Apolloni,E.; Valle, G.; Lanfranchi, G.; Danieli, G. A.: Chromosomal localizationof the human genes, CPP32, Mch2, Mch3, and Ich-1, involved in cellularapoptosis. Biochem. Biophys. Res. Commun. 225: 983-989, 1996.

[0725] 323.Woo, M.; Hakem, R.; Soengas, M. S.; Duncan, G. S.; Shahinian,A.; Kagi, K.; Hakem, A.; McCurrach, M.; Khoo, W.; Kaufman, S. A.;Senaldi, G.; Howard, T.; Lowe, S. W.;

Mak, T. W.: Essential contributionof caspase 3/CPP32 to apoptosis and its associated nuclear changes. GenesDev. 12: 806-819, 1998.

[0726] 324.Nicholson, D. W.; Ali, A.; Thornberry, N. A.; Vaillancourt, J.P.; Ding, C. K.; Gallant, M.; Gareau, Y.; Griffin, P. R.; Labelle,M.; Lazebnik, Y. A.; Munday, N. A.; Raju, S. M.; Smulson, M. E.; Yamin,T.-T.; Yu, V. L.; Miller, D. K.: Identification and inhibition ofthe ICE/CED-3 protease necessary for mammalian apoptosis. Nature 376:37-43, 1995. MEDLINE UID: 95319529

[0727] 325.Geurts, J. M. W.; Schoenmakers, E. F. P. M.; Roijer, E.; Astrom,A.-K.; Stenman, G.; van de Ven, W. J. M.: Identification of NFIBas recurrent translocation partner gene of HMGIC in pleomorphic adenomas. Oncogene 16:865-872, 1998.

[0728] 326.Becker, P. E.: Two new families of benign sex-linked recessivemuscular dystrophy. Rev. Canad. Biol. 21: 551-566, 1962.

[0729] 327.Becker, P. E.: Eine neue X-chromosomale Muskeldystrophie. ActaPsychiat. Neurol. Scand. 193: 427, 1955.

[0730] 328.Becker, P. E.: Neue Ergebnisse der Genetik der Muskeldystrophien. ActaGenet. Statist. Med. 7: 303-310, 1957.

[0731] 329.Bushby, K. M. D.; Cleghorn, N. J.; Curtis, A.; Haggerty, I. D.;Nicholson, L. V. B.; Johnson, M. A.; Harris, J. B.; Bhattacharya,S. S.: Identification of a mutation in the promoter region of thedystrophin gene in a patient with atypical Becker muscular dystrophy. Hum.Genet. 88: 195-199, 1991.

[0732] 330.Doriguzzi, C.; Palmucci, L.; Mongini, T.; Chiado-Piat, L.; Restagno,G.; Ferrone, M.: Exercise intolerance and recurrent myoglobinuriaas the only expression of Xp21 Becker type muscular dystrophy. J.Neurol. 240: 269-271, 1993.

[0733] 331.England, S. B.; Nicholson, L. V. B.; Johnson, M. A.; Forrest,S. M.; Love, D. R.; Zubrzycka-Gaarn, E. E.; Bulman, D. E.; Harris,J. B.; Davies, K. E.: Very mild muscular dystrophy associated withthe deletion of 46% dystrophin. Nature 343: 180-182, 1990.

[0734] 332.Bodrug, S. E.; Ray, P. N.; Gonzalez, I. L.; Schmickel, R. D.;Sylvester, J. E.; Worton, R. G.: Molecular analysis of a constitutionalX-autosome translocation in a female with muscular dystrophy. Science 237:1620-1624, 1987.

[0735] 333.Boyce, F. M.; Beggs, A. H.; Feener, C.; Kunkel, L. M.: Dystrophinis transcribed in brain from a distant upstream promoter. Proc. Nat.Acad. Sci. 88: 1276-1280, 1991.

[0736] 334.Boyd, Y.; Buckle, V. J.: Cytogenetic heterogeneity of translocationsassociated with Duchenne muscular dystrophy. Clin. Genet. 29: 108-115,1986.

[0737] 335.Bulman, D. E.; Gangopadhyay, S. B.; Bebchuck, K. G.; Worton, R.G.; Ray, P. N.: Point mutation in the human dystrophin gene: identificationthrough Western blot analysis. Genomics 10: 457-460, 1991.

[0738] 336.Burke, J. F.; Mogg, A. E.: Suppression of a nonsense mutationin mammalian cells in vivo by the aminoglycoside antibiotics G-418and paromomycin. Nucleic Acids Res. 13: 6265-6272, 1985.

[0739] 337.Burnette, W. N.: 'Western blotting': electrophoretic transferof proteins from sodium dodecyl sulfate-polyacrylamide gels to unmodifiednitrocellulose and radiographic detection with antibody and radioiodinated-protein A. Anal. Biochem. 112: 195-203, 1981.

[0740] 338.Chamberlain, J. S.; Pearlman, J. A.; Muzny, D. M.; Gibbs, R. A.;Ranier, J. E.; Reeves, A. A.; Caskey, C. T.: Expression of the murineDuchenne muscular dystrophy gene in muscle and brain. Science 239:1416-1418, 1988.

[0741] 339.Chelly, J.; Concordet, J.-P.; Kaplan, J.-C.; Kahn, A.: Illegitimatetranscription: transcription of any gene in any cell type. Proc.Nat. Acad. Sci. 86: 2617-2621, 1989.

[0742] 340.Chelly, J.; Gilgenkrantz, H.; Hugnot, J. P.; Hamard, G.; Lambert,M.; Recan, D.; Akli, S.; Cometto, M.; Kahn, A.; Kaplan, J. C.: Illegitimatetranscription: application to the analysis of truncated transcriptsof the dystrophin gene in nonmuscle cultured cells from Duchenne andBecker patients. J. Clin. Invest. 88: 1161-1166, 1991.

[0743] 341.Chelly, J.; Hamard, G.; Koulakoff, A.; Kaplan, J.-C.; Kahn, A.;Berwald-Netter, Y.: Dystrophin gene transcribed from different promotersin neuronal and glial cells. Nature 344: 64-65, 1990.

[0744] 342.Chelly, J.; Kaplan, J.-C.; Maire, P.; Gautron, S.; Kahn, A.:Transcription of the dystrophin gene in human muscle and non-muscletissues. Nature 333: 858-860, 1988.

[0745] 343.Clemens, P. R.; Ward, P. A.; Caskey, C. T.; Bulman, D. E.; Fenwick,R. G.: Premature chain termination mutation causing Duchenne musculardystrophy. Neurology 42: 1775-1782, 1992.

[0746] 344.Cooper, B. J.; Valentine, B. A.; Wilson, S.; Patterson, D. F.;Concannon, P. W.: Canine muscular dystrophy: confirmation of X-linkedinheritance. J. Hered. 79: 405-408, 1988.

[0747] 345.Covone, A. E.; Lerone, M.; Romeo, G.: Genotype-phenotype correlationand germline mosaicism in DMD/

BMD patients with deletions of the dystrophingene. Hum. Genet. 87: 353–360, 1991.

[0748] 346.Cox, G. A.; Cole, N. M.; Matsumura, K.; Phelps, S. F.; Hauschka,S. D.; Campbell, K. P.; Faulkner, J. A.; Chamberlain, J. S.: Overexpressionof dystrophin in transgenic mdx mice eliminates dystrophic symptomswithout toxicity. Nature 364: 725–729, 1993.

[0749] 347.Cox, G. A.; Sunada, Y.; Campbell, K. P.; Chamberlain, J. S.:Dp71 can restore the dystrophin-associated glycoprotein complex inmuscle but fails to prevent dystrophy. Nature Genet. 8: 333–339,1994.

[0750] 348.Comi, G. P.; Ciafaloni, E.; de Silva, H. A. R.; Prelle, A.; Bardoni,A.; Rigoletto, C.; Robotti, M.; Bresolin, N.; Moggio, M.; Fortunato,F.; Ciscato, P.; Turconi, A.; Rose, A. D.; Scarlato, G.: A G(+1)-to-Atransversion at the 5-prime splice site of intron 69 of the dystrophingene causing the absence of peripheral nerve Dp116 and severe clinicalinvolvement in a DMD patient. Hum. Molec. Genet. 4: 2171–2174, 1995.

[0751] 349.Crawford, G. E.; Lu, Q. L.; Partridge, T. A.; Chamberlain, J.S.: Suppression of revertant fibers in mdx mice by expression ofa functional dystrophin. Hum. Molec. Genet. 10: 2745–2750, 2001.

[0752] 350.Darras, B. T.; Blattner, P.; Harper, J. F.; Spiro, A. J.; Alter,S.; Francke, U.: Intragenic deletions in 21 Duchenne muscular dystrophy(DMD)/Becker muscular dystrophy (BMD) families studied with the dystrophincDNA: location of breakpoints on HindIII and BglII exon-containingfragment maps, meiotic and mitotic origin of the mutations. Am. J.Hum. Genet. 43: 620-629, 1988.

[0753] 351.Darras, B. T.; Francke, U.: Normal human genomic restriction-fragmentpatterns and polymorphisms revealed by hybridization with the entiredystrophin cDNA. Am. J. Hum. Genet. 43: 612-619, 1988.

[0754] 352.Darras, B. T.; Francke, U.: A partial deletion of the musculardystrophy gene transmitted twice by an unaffected male. Nature 329:556-558, 1987.

[0755] 353.Davies, K. E.; Smith, T. J.; Bundey, S.; Read, A. P.; Flint, T.;Bell, M.; Speer, A.: Mild and severe muscular dystrophy associatedwith deletions in Xp21 of the human X chromosome. J. Med. Genet. 25:9-13, 1988.

[0756] 354.De Angelis, F. G.; Sthandier, O.; Berarducci, B.; Toso, S.; Galluzzi,G.; Ricci, E.; Cossu, G.; Bozzoni, I.: Chimeric snRNA molecules carryingantisense sequences against the splice junctions of exon 51 of thedystrophin pre-mRNA induce exon skipping and restoration of a dystrophinsyn-

thesis in delta-48-50 DMD cells. Proc Nat. Acad. Sci. 99: 9456-9461,2002.

[0757] 355.den Dunnen, J. T.; Bakker, E.; Klein Breteler, E. G.; Pearson,P. L.; van Ommen, G. J. B.: Direct mutation of more than 50% of theDuchenne muscular dystrophy mutations by field inversion gels. Nature 329:640-642, 1987.

[0758] 356.Dickson, G.; Pizzey, J. A.; Elsom, V. E.; Love, D.; Davies, K.E.; Walsh, F. S.: Distinct dystrophin mRNA species are expressedin embryonic and adult mouse skeletal muscle. FEBS Lett. 242: 47-52,1988.

[0759] 357.Dominguez-Steglich, M.; Meng, G.; Bettecken, T.; Muller, C. R.;Schmid, M.: The dystrophin gene is autosomally located on a microchromosomein chicken. Genomics 8: 536-540, 1990.

[0760] 358.Doolittle, R. F.: Similar amino acid sequences: chance or commonancestry? Science 214: 149-159, 1981.

[0761] 359.Dubrovsky, A. L.; Taratuto, A. L.; Sevlever, G.; Schultz, M.;Pegoraro, E.; Hoop, R. C.; Hoffman, E. P.: Duchenne muscular dystrophyand myotonic dystrophy in the same patient. Am. J. Med. Genet. 55:342-348, 1995.

[0762] 360.Emery, A. E. H.: Duchenne Muscular Dystrophy. Oxford, UK: OxfordUniversity Press (pub.) (2nd ed.): 1993.

[0763] 361.Fabb, S. A.; Wells, D. J.; Serpente, P.; Dickson, G.: Adeno-associatedvirus vector gene transfer and sarcolemmal expression of a 144 kDamicro-dystrophin effectively restores the dystrophin-associated proteincomplex and inhibits myofibre degeneration in nude/mdx mice. Hum.Molec. Genet. 11: 733-741, 2002.

[0764] 362.Feener, C. A.; Boyce, F. M.; Kunkel, L. M.: Rapid detection ofCA polymorphisms in cloned DNA: application to the 5-prime regionof the dystrophin gene. Am. J. Hum. Genet. 48: 621-627, 1991.

[0765] 363.Ferlini, A.; Galie, N.; Merlini, L.; Sewry, C.; Branzi, A.; Muntoni,F.: A novel Alu-like element rearranged in the dystrophin gene causesa splicing mutation in a family with X-linked dilated cardiomyopathy. Am.J. Hum. Genet. 63: 436-446, 1998.

[0766] 364.Finnegan, D. J.: Eukaryotic transposable elements and genomeevolution. Trends Genet. 5: 103-107, 1989.

[0767] 365.Forrest, S. M.; Cross, G. S.; Speer, A.; Gardner-Medwin, D.; Burn,J.; Davies, K. E.: Preferential deletion of exons in Duchenne andBecker muscular dystrophies. Nature 329: 638-640, 1987.

[0768] 366.Francke, U.; Ochs, H. D.; de Martinville, B.; Giacalone, J.; Lindgren,V.; Disteche, C.; Pagon, R. A.; Hofker, M. H.;

van Ommen, G.-J. B.;Pearson, P. L.; Wedgwood, R. J.: Minor Xp21 chromosome deletion ina male associated with expression of Duchenne muscular dystrophy,chronic granulomatous disease, retinitis pigmentosa, and McLeod syndrome. Am.J. Hum. Genet. 37: 250-267, 1985.

[0769] 367.Furst, D.; Nave, R.; Osborn, M.; Weber, K.; Bardosi, A.; Archidiacono,N.; Ferro, M.; Romano, V.; Romeo, G.: Nebulin and titin expressionin Duchenne muscular dystrophy appears normal. FEBS Lett. 224: 49-53,1987.

[0770] 368.Giacalone, J. P.; Francke, U.: Common sequence motifs at therearrangement sites of a constitutional X/autosome translocation andassociated deletion. Am. J. Hum. Genet. 50: 725-741, 1992.

[0771] 369.Gillard, E. F.; Chamberlain, J. S.; Murphy, E. G.; Duff, C. L.;Smith, B.; Burghes, A. H. M.; Thompson, M. W.; Sutherland, J.; Oss,I.; Bodrug, S. E.; Klamut, H. J.; Ray, P. N.; Worton, R. G.: Molecularand phenotypic analysis of patients with deletions within the deletion-richregion of the Duchenne muscular dystrophy (DMD) gene. Am. J. Hum.Genet. 45: 507-520, 1989.

[0772] 370.Ginjaar, I. B.; Kneppers, A. L. J.; Meulen, J.-D. M.; Anderson,L. V. B.; Bremmer-Bout, M.; van Deutekom, J. C. T.; Weegenaar, J.;den Dunnen, J. T.; Bakker, E.: Dystrophin

nonsense mutation inducesdifferent levels of exon 29 skipping and leads to variable phenotypeswithin one BMD family. Europ. J. Hum. Genet. 8: 793–796, 2000.

[0773] 371.Greenberg, D. S.; Sunada, Y.; Campbell, K. P.; Yaffe, D.; Nudel,U.: Exogenous Dp71 restores the levels of dystrophin associated proteinsbut does not alleviate muscle damage in mdx mice. Nature Genet. 8:340–344, 1994.

[0774] 372.Gussoni, E.; Soneoka, Y.; Strickland, C. D.; Buzney, E. A.; Khan,M. K.; Flint, A. F.; Kunkel, L. M.; Mulligan, R. C.: Dystrophin expressionin the mdx mouse restored by stem cell transplantation. Nature 401:390–394, 1999.

[0775] 373.Hagiwara, Y.; Mizuno, Y.; Takemitsu, M.; Matsuzaki, T.; Nonaka,I.; Ozawa, E.: Dystrophin-positive muscle fibers following C2 myoblasttransplantation into mdx nude mice. Acta Neuropath. 90: 592–600,1995.

[0776] 374.Hagiwara, Y.; Nishio, H.; Kitoh, Y.; Takeshima, Y.; Narita, N.;Wada, H.; Yokoyama, M.; Nakamura, H.; Matsuo, M.: A novel point mutation(G(-1) to T) in a 5-prime splice donor site of intron 13 of the dystrophingene results in exon skipping and is responsible for Becker musculardystrophy. Am. J. Hum. Genet. 54: 53–61, 1994.

[0777] 375.Hammonds, R. G., Jr.: Protein sequence of DMD gene is relatedto actin-binding domain of alpha-actinin.

(Letter) Cell 51: 1, 1987.

[0778] 376.Harper, S. Q.; Hauser, M. A.; DelloRusso, C.; Duan, D.; Crawford,R. W.; Phelps, S. F.; Harper, H. A.; Robinson, A. S.; Engelhardt,J. F.; Brooks, S. V.; Chamberlain, J. S.: Modular flexibility ofdystrophin: implications for gene therapy of Duchenne muscular dystrophy. NatureMed. 8: 253-261, 2002.

[0779] 377.Hart, K. A.; Hodgson, S.; Walker, A.; Cole, C. G.; Johnson, L.;Dubowitz, V.; Bobrow, M.: DNA deletions in mild and severe Beckermuscular dystrophy. Hum. Genet. 75: 281-285, 1987.

[0780] 378.Hodgson, S. V.; Abbs, S.; Clark, S.; Manzur, A.; Heckmatt, J.Z. H.; Dubowitz, V.; Bobrow, M.: Correlation of clinical and deletiondata in Duchenne and Becker muscular dystrophy, with special referenceto mental ability. Neuromusc. Disord. 2: 269-276, 1992.

[0781] 379.Hoffman, E. P.; Brown, R. H., Jr.; Kunkel, L. M.: The proteinproduct of the Duchenne muscular dystrophy locus. Cell 51: 919-928,1987.

[0782] 380.Hoffman, E. P.; Knudson, C. M.; Campbell, K. P.; Kunkel, L. M.: Subcellular fractionation of dystrophin to the triads of skeletalmuscle. Nature 330: 754-758, 1987.

[0783] 381.Hoffman, E. P.; Monaco, A. P.; Feener, C. C.; Kunkel,

L. M.:Conservation of the Duchenne muscular dystrophy gene in mice and humans. Science 238:347–350, 1987.

[0784] 382.Hoop, R. C.; Russo, L. S.; Riconda, D. L.; Schwartz, L. S.; Hoffman,E. P.: Restoration of half the normal dystrophin sequence in a double-deletionDuchenne muscular dystrophy family. Am. J. Med. Genet. 49: 323–327,1994.

[0785] 383.Hoffman, E. P.; Fischbeck, K. H.; Brown, R. H.; Johnson, M.; Medori,R.; Loike, J. D.; Harris, J. B.; Waterston, R.; Brooke, M.; Specht,L.; Kupsky, W.; Chamberlain, J.; Caskey, C. T.; Shapiro, F.; Kunkel,L. M.: Characterization of dystrophin in muscle-biopsy specimensfrom patients with Duchenne's or Becker's muscular dystrophy. NewEng. J. Med. 318: 1363–1368, 1988.

[0786] 384.Howard, P. L.; Dally, G. Y.; Wong, M. H.; Ho, A.; Weleber, R.G.; Pillers, D.-A. M.; Ray, P. N.: Localization of dystrophin isoformDp71 to the inner limiting membrane of the retina suggests a uniquefunctional contribution of Dp71 in the retina. Hum. Molec. Genet. 7:1385–1391, 1998.

[0787] 385.Hu, X.; Burghes, A. H. M.; Bulman, D. E.; Ray, P. N.; Worton,R. G.: Evidence for mutation by unequal sister chromatid exchangein the Duchenne muscular dystrophy gene. Am. J. Hum. Genet. 44:855–863, 1989.

[0788] 386.Kedra, D.; Pan, H.-Q.; Seroussi, E.; Fransson, I.; Guilbaud, C.;Collins, J. E.; Dunham, I.; Blennow, E.; Roe, B. A.; Piehl, F.; Dumanski,J. P.: Characterization of the human synaptogyrin gene family. Hum.Genet. 103: 131-141, 1998.

[0789] 387.Fischle, W.; Emiliani, S.; Hendzel, M. J.; Nagase, T.; Nomura,N.; Voelter, W.; Verdin, E.: A new family of human histone deacetylasesrelated to Saccharomyces cerevisiae HDA1p. J. Biol. Chem. 274: 11713-11720,1999.

[0790] 388.Pazin, M. J.; Kadonaga, J. T.: What's up and down with histonedeacetylation and transcription? Cell 89: 325-328, 1997.

[0791] 389.Uchiumi, T.; Hinoshita, E.; Haga, S.; Nakamura, T.; Tanaka, T.;Toh, S.; Furukawa, M.; Kawabe, T.; Wada, M.; Kagotani, K.; Okumura,K.; Kohno, K.; Akiyama, S.; Kuwano, M.: Isolation of a novel humancanalicular multi-specific organic anion transporter, cMOAT2/MRP3,and its expression in cisplatin-resistant cancer cells with de-creasedATP-dependent drug transport. Biochem. Biophys. Res. Commun. 252:103-110, 1998.

[0792] 390.Arriza, J. L.; Kavanaugh, M. P.; Fairman, W. A.; Wu, Y.-N.; Murdoch,G. H.; North, R. A.; Amara, S. G.: Cloning and expression of a humanneutral amino acid transporter

with structural similarity to the glutamatetransporter gene family. J. Biol. Chem. 268: 15329-15332, 1993.

[0793] 391.Hofmann, K.; Duker, M.; Fink, T.; Lichter, P.; Stoffel, W.: Humanneutral amino acid transporter ASCT1: structure of the gene (SLC1A4)and localization to chromosome 2p13-p15. Genomics 24: 20-26, 1994.

[0794] 392.Shafqat, S.; Tamarappoo, B. K.; Kilberg, M. S.; Puranam, R. S.;McNamara, J. O.; Guadano-Ferraz, A.; Fremeau, R. T., Jr.: Cloningand expression of a novel Na(+)-dependent neutral amino acid transporterstructurally related to mammalian Na(+)/glutamate cotransporters. J.Biol. Chem. 268: 15351-15355, 1993.

[0795] 393.Zerangue, N.; Kavanaugh, M. P.: ASCT-1 is a neutral amino acidexchanger with chloride channel activity. J. Biol. Chem. 271: 27991-27994,1996.

[0796] 394.Schwientek, T.; Nomoto, M.; Levery, S. B.; et al: Control of O-glycanbranch formation. J. Biol. Chem. 274: 4504-4512, 1999.

[0797] 395.Nonaka, S.; Tanaka, Y.; Okada, Y.; Takeda, S.; Harada, A.; Kanai,Y.; Kido, M.; Hirokawa, N.: Randomization of left-right asymmetrydue to loss of nodal cilia generating leftward flow of extraembryonicfluid in mice lacking KIF3B motor protein. Cell 95: 829-837, 1998.

[0798] 396.Yamazaki, H.; Nakata, T.; Okada, Y.; Hirokawa, N.: KIF3A/B: aheterodimeric kinesin superfamily protein that works as a microtubuleplus end-directed motor for membrane organelle transport. J. CellBiol. 130: 1387-1399, 1995.

[0799] 397.Akao, Y.; Matsuda, Y.: Identification and chromosome mapping ofthe mouse homologue of the human gene (DDX6) that encodes a putativeRNA helicase of the DEAD box protein family. Cytogenet. Cell Genet. 75:38-44, 1996.

[0800] 398.Akao, Y.; Seto, M.; Takahashi, T.; Kubonishi, I.; Miyoshi, I.;Nakazawa, S.; Tsujimoti, Y.; Croce, C. M.; Ueda, R.: Molecular cloningof the chromosomal breakpoint of a B-cell lymphoma with the t(11;14)(q23;q32)chromosome translocation. Cancer Res. 51: 1574-1576, 1991.

[0801] 399.Akao, Y.; Seto, M.; Yamamoto, K.; Iida, S.; Nakazawa, S.; Inazawa,J.; Abe, T.; Takahashi, T.; Ueda, R.: The RCK gene associated witht(11;14) translocation is distinct from the MLL/ALL-1 gene with t(4;11)and t(11;19) translocations. Cancer Res. 52: 6083-6087, 1992.

[0802] 400.Akao, Y.; Tsujimoto, Y.; Finan, J.; Nowell, P. C.; Croce, C. M.: Molecular characterization of a t(11;14)(q23;q32) chromosome translocationin a B-cell lymphoma. Cancer

Res. 50: 4856–4859, 1990.

[0803] 401.Lu, D.; Yunis, J. J.: Cloning, expression and localiza-
tion ofan RNA helicase gene from a human lymphoid cell
line with chromosomalbreakpoint 11q23.3. Nucleic Acids
Res. 20: 1967–1972, 1992.

[0804] 402.Seto, M.; Yamamoto, K.; Takahashi, T.; Ueda, R.:
Cloning and expressionof a murine cDNA homologous to
the human RCK/P54, a lymphoma-linkedchromosomal
translocation junction gene on 11q23. Gene 166:
293–296,1995.

[0805] 403.Tunnacliffe, A.; Perry, H.; Radice, P.; Budarf, M. L.;
Emanuel,B. S.: A panel of sequence tagged sites for chro-
mosome band 11q23. Genomics 17:744–747, 1993.

[0806] 404.Abbs, S.; Roberts, R. G.; Mathew, C. G.; Bentley, D. R.;
Bobrow,M.: Accurate assessment of intragenic recombina-
tion frequency withinthe Duchenne muscular dystrophy
gene. Genomics 7: 602–606, 1990.

[0807] 405.Ahn, A. H.; Kunkel, L. M.: The structural and func-
tional diversityof dystrophin. Nature Genet. 3: 283–291,
1993.

[0808] 406.Alwine, J. C.; Kemp, D. J.; Stark, G. R.: Method for de-
tectionof specific RNAs in agarose gels by transfer to dia-
zobenzyloxymethyl-paperand by hybridization with DNA

probes. Proc. Nat. Acad. Sci. 74:5350–5354, 1977.

[0809] 407.Angelini, C.; Beggs, A. H.; Hoffman, E. P.; Fanin, M.; Kunkel,L. M.: Enormous dystrophin in a patient with Becker muscular dystrophy. Neurology 40:808–812, 1990.

[0810] 408.Badorff, C.; Berkely, N.; Mehrotra, S.; Talhouk, J. W.; Rhoads,R. E.; Knowlton, K. U.: Enteroviral protease 2A directly cleavesdystrophin and is inhibited by a dystrophin-based substrate analogue. J.Biol. Chem. 275: 11191–11197, 2000.

[0811] 409.Badorff, C.; Lee, G.-H.; Lamphear, B. J.; Martone, M. E.; Campbell,K. P.; Rhoads, R. E.; Knowlton, K. U.: Enteroviral protease 2A cleavesdystrophin: evidence of cytoskeletal disruption in an acquired cardiomyopathy. NatureMed. 5: 320–326, 1999.

[0812] 410.Bakker, E.; Pearson, P. L.: Mutation of the Duchenne musculardystrophy gene associated with meiotic recombination. (Letter) Clin.Genet. 30: 347–349, 1986.

[0813] 411.Bakker, E.; Hofker, M. H.; Goor, N.; Mandel, J. L.; Wrogemann,K.; Davies, K. E.; Kunkel, L. M.; Willard, H. F.; Fenton, W. A.; Sandkuyl,L.; Majoor-Krakauer, D.; van Essen, A. J.; Jahoda, M. G. J.; Sachs,E. S.; van Ommen, G. J. B.; Pearson, P. L.: Prenatal diagnosis andcarrier detection of Duchenne muscular dystrophy with closely linkedRFLPs.

Lancet I: 655–658, 1985.

[0814] 412.Bakker, E.; Van Broeckhoven, C.; Bonten, E. J.; van de Vooren,M. J.; Veenema, H.; Van Hul, W.; Van Ommen, G. J. B.; Vandenberghe,A.; Pearson, P. L.: Germline mosaicism and Duchenne muscular dystrophymutations. Nature 329: 554–556, 1987.

[0815] 413.Bar, S.; Barnea, E.; Levy, Z.; Neuman, S.; Yaffe, D.; Nudel, U.: A novel product of the Duchenne muscular dystrophy gene which greatlydiffers from the known isoforms in its structure and tissue distribution. Biochem.J. 272: 557–560, 1990.

[0816] 414.Barbieri, A. M.; Soriani, N.; Tubiello, G. M.; Ferrari, M.; Carrera,P.: A nonsense mutation (gln–673–term) in exon 17 of the human dystrophingene detected by heteroduplex analysis. Hum. Genet. 96: 343–344,1995.

[0817] 415.Bartlett, R. J.; Pericak–Vance, M. A.; Koh, J.; Yamaoka, L. H.;Chen, J. C.; Hung, W.–Y.; Speer, M. C.; Wapenaar, M. C.; Van Ommen,G. J. B.; Bakker, E.; Pearson, P. L.; Kandt, R. S.; Siddique, T.;Gilbert, J. R.; Lee, J. E.; Sirotkin–Roses, M. J.; Roses, A. D.:Duchenne muscular dystrophy: high frequency of deletions. Neurology 38:1–4, 1988.

[0818] 416.Barton–Davis, E. R.; Cordier, L.; Shoturma, D. I.; Leland, S.E.; Sweeney, H. L.: Aminoglycoside antibiotics re-

store dystrophinfunction to skeletal muscles of mdx mice. J. Clin. Invest. 104:375-381, 1999.

[0819] 417.Bastianutto, C.; Bestard, J. A.; Lahnakoski, K.; Broere, D.; DeVisser, M.; Zaccolo, M.; Pozzan, T.; Ferlini, A.; Muntoni, F.; Patarnello,T.; Klamut, H. J.: Dystrophin muscle enhancer 1 is implicated inthe activation of non-muscle isoforms in the skeletal muscle of patientswith X-linked dilated cardiomyopathy. Hum. Molec. Genet. 10: 2627-2635,2001.

[0820] 418.Baumbach, L. L.; Chamberlain, J. S.; Ward, P. A.; Far-well, N.J.; Caskey, C. T.: Molecular and clinical correlation of deletionleading to Duchenne and Becker muscular dystrophies. Neurology 39:465-474, 1989.

[0821] 419.Baumbach, L. L.; Ward, P. A.; Fenwick, R.; Caskey, C. T.: Analysisof mutations at the Duchenne muscular dystrophy locus provides noevidence for illegitimate recombination in deletion formation. (Abstract) Am.J. Hum. Genet. 45 (suppl.): A173, 1989.

[0822] 420.Beggs, A. H.; Koenig, M.; Boyce, F. M.; Kunkel, L. M.: Detectionof 98% of DMD/BMD gene deletions by polymerase chain reaction. Hum.Genet. 86: 45-48, 1990.

[0823] 421.Berko, B. A.; Swift, M.: X-linked dilated cardiomyopathy. NewEng. J. Med. 316: 1186-1191, 1987.

[0824] 422.Bettecken, T.; Muller, C. R.: Identification of a 220-kb insertioninto the Duchenne gene in a family with an atypical course of musculardystrophy. Genomics 4: 592-596, 1989.

[0825] 423.Bies, R. D.: X-linked dilated cardiomyopathy. (Letter) New Eng.J. Med. 330: 368-369, 1994.

[0826] 424.Bies, R. D.; Caskey, C. T.; Fenwick, R.: An intact cysteine-richdomain is required for dystrophin function. J. Clin. Invest. 90:666-672, 1992.

[0827] 425.Bittner, R. E.; Streubel, B.; Shorny, S.; Schaden, G.; Voit, T.;Hoger, H.: Coisogenic all-plus-one immunization: a model for identifyingmissing proteins in null-mutant conditions. Antibodies to dystrophinin mdx mouse after transplantation of muscle from normal coisogenicdonor. Neuropediatrics 25: 176-182, 1994.

[0828] 426.Abuladze, N.; Lee, I.; Newman, D.; Hwang, J.; Boorer, K.; Pushkin,A.; Kurtz, I.: Molecular cloning, chromosomal localization, tissuedistribution, and functional expression of the human pancreatic sodiumbicarbonate cotransporter. J. Biol. Chem. 273: 17689-17695, 1998.

[0829] 427.Burnham, C. E.; Amlal, H.; Wang, Z.; Shull, G. E.; Soleimani, M.: Cloning and functional expression of a human kidney Na+:HCO3- cotransporter. J.Biol. Chem. 272:

19111-19114, 1997.

[0830] 428.Choi, I.; Romero, M. F.; Khandoudi, N.; Bril, A.; Boron, W. F.: Cloning and characterization of a human electrogenic Na(+)-HCO(3-)cotransporter isoform (hhNBC). Am. J. Physiol. 276: C576-C584, 1999.

[0831] 429.Igarashi, T.; Inatomi, J.; Sekine, T.; Cha, S. H.; Kanai, Y.; Kunimi,M.; Tsukamoto, K.; Satoh, H.; Shimadzu, M.; Tozawa, F.; Mori, T.;Shiobara, M.; Seki, G.; Endou, H.: Mutations in SLC4A4 cause permanentisolated proximal renal tubular acidosis with ocular abnormalities.(Letter) Nature Genet. 23: 264-265, 1999.

[0832] 430.Romero, M. F.; Boron, W. F.: Electrogenic Na(+)/HCO(3-) cotransporters:cloning and physiology. Annu. Rev. Physiol. 61: 699-723, 1999.

[0833] 431.Soleimani, M.; Burnham, C. E.: Physiologic and molecular aspectsof the Na(+):HCO(3-) cotransporter in health and disease processes. KidneyInt. 57: 371-384, 2000.

[0834] 432.Usui, T.; et al.; et al. :Pflugers Arch. 438: 458-462, 1999.

[0835] 433.Hirohata, S.; Seldin, M. F.; Apte, S. S.: Chromosomal assignmentof two ADAM genes, TACE (ADAM17) and MLTNB (ADAM19), to human chromosomes2 and 5, respectively, and of Mltnb to mouse chromosome 11. Ge-

nomics 54:178–179, 1998.

[0836] 434. Inoue, D.; Reid, M.; Lum, L.; Kratzschmar, J.; Weskamp, G.; Myung,Y. M.; Baron, R.; Blobel, C. P.: Cloning and initial characterizationof mouse meltrin beta and analysis of the expression of four metalloprotease-disintegrinsin bone cells. J. Biol. Chem. 273: 4180–4187, 1998.

[0837] 435. Kools, P.; Van Imschoot, G.; van Roy, F.: Characterization ofthree novel human cadherin genes (CDH7, CDH19, and CDH20) clusteredon chromosome 18q22–q23 and with high homology to chicken cadherin-7. Genomics 68:283–295, 2000.

[0838] 436. Janz, R.; Sudhof, T. C.; Hammer, R. E.; Unni, V.; Siegelbaum, S.A.; Bolshakov, V. Y.: Essential roles in synaptic plasticity forsynaptogyrin I and synaptophysin I. Neuron 24: 687–700, 1999.

[0839] 437. McMahon, H. T.; Bolshakov, V. Y.; Janz, R.; Hammer, R. E.; Siegelbaum,S. A.; Sudhof, T. C.: Synaptophysin, a major synaptic vesicle protein,is not essential for neurotransmitter release. Proc. Nat. Acad. Sci. 93:4760–4764, 1996.

[0840] 438. Engelender, S.; Wanner, T.; Kleiderlein, J. J.; Wakabayashi, K.;Tsuji, S.; Takahashi, H.; Ashworth, R.; Margo-

lis, R. L.; Ross, C.A.: Organization of the human synphilin-1 gene, a candidate for Parkinson'sdisease. Mammalian Genome 11: 763-766, 2000.

[0841] 439.Mach, B.; Steimle, V.; Martinez-Soria, E.; Reith, W.: Regulationof MHC class II genes: lessons from a disease. Annu. Rev. Immun. 14:301-331, 1996.

[0842] 440.Scholl, T.; Mahanta, S. K.; Strominger, J. L.: Specific complexformation between the type II bare lymphocyte syndrome-associatedtransactivators CIITA and RFX5. Proc. Nat. Acad. Sci. 94: 6330-6334,1997.

[0843] 441.Emery, P.; Durand, B.; Mach, B.; Reith, W.: RFX proteins, a novelfamily of DNA binding proteins conserved in the eukaryotic kingdom. NucleicAcids Res. 24: 803-807, 1996.

[0844] 442.Braverman, N.; Lin, P.; Moebius, F. F.; Obie, C.; Moser, A.; Glossmann,H.; Wilcox, W. R.; Rimoin, D. L.; Smith, M.; Kratz, L.; Kelley, R.I.; Valle, D.: Mutations in the gene encoding 3-beta-hydroxysteroid-delta(8),delta(7)-isomerasecause X-linked dominant Conradi-Hunermann syndrome. Nature Genet. 22:291-294, 1999.

[0845] 443.Cho, S. Y.; Kim, J. H.; Paik, Y. K.: Cholesterol biosynthesisfrom lanosterol: differential inhibition of sterol delta

8-isomeraseand other lanosterol-converting enzymes by tamoxifen. Molec. Cells 8:233-239, 1998.

[0846] 444.Clayton, P. T.; Kalter, D. C.; Atherton, D. J.; Besley, G. T.;Broadhead, D. M.: Peroxisomal enzyme deficiency in X-linked dominantConradi-Hunermann syndrome. J. Inherit. Metab. Dis. 12: 358-360,1989.

[0847] 445.Derry, J. M. J.; Gormally, E.; Means, G. D.; Zhao, W.; Meindl,A.; Kelley, R. I.; Boyd, Y.; Herman, G. E.: Mutations in a delta(8)-delta(7)sterol isomerase in the tattered mouse and X-linked dominant chondrodysplasiapunctata. Nature Genet. 22: 286-290, 1999.

[0848] 446.Grange, D. K.; Kratz, L. E.; Braverman, N. E.; Kelley, R. I.:CHILD syndrome caused by deficiency of 3-beta-hydroxysteroid-delta-8,delta-7-isomerase. Am.J. Med. Genet. 90: 328-335, 2000.

[0849] 447.Hanner, M.; Moebius, F. F.; Weber, F.; Grabner, M.; Striessnig,J.; Glossmann, H.: Phenylalkylamine Ca(2+) antagonist binding protein:molecular cloning, tissue distribution, and heterologous expression. J.Biol. Chem. 270: 7551-7557, 1995.

[0850] 448.Has, C.; Bruckner-Tuderman, L.; Muller, D.; Floeth, M.; Folkers,E.; Donnai, D.; Traupe, H.: The Conradi-Hunermann-Happle syndrome(CDPX2) and emopamil

binding protein: novel mutations, and somaticand gonadal mosaicism. Hum. Molec. Genet. 9: 1951–1955, 2000.

[0851] 449.Holmes, R. D.; Wilson, G. N.; Hajra, A. K.: Peroxisomal enzymedeficiency in the Conradi–Hunerman (sic) form of chondrodysplasiapunctata. New Eng. J. Med. (Letter) 316: 1608 only, 1987.

[0852] 450.Ikegawa, S.; Ohashi, H.; Ogata, T.; Honda, A.; Tsuka-hara, M.; Kubo,T.; Kimizuka, M.; Shimode, M.; Hasegawa, T.; Nishimura, G.; Nakamura,Y.: Novel and recurrent EBP mutations in X-linked dominant chondrodysplasiapunc-tata. Am. J. Med. Genet. 94: 300–305, 2000.

[0853] 451.Kelley, R. I.; Wilcox, W. G.; Smith, M.; Kratz, L. E.; Moser,A.; Rimoin, D. S.: Abnormal sterol metabolism in patients with Conradi–Hunermann–Happlesyndrome and sporadic lethal chondrodysplasia punctata. Am. J. Med.Genet. 83: 213–219, 1999.

[0854] 452.Eudy, J. D.; Yao, S.; Weston, M. D.; Ma-Edmonds, M.; Talmadge,C. B.; Cheng, J. J.; Kimberling, W. J.; Sumegi, J.: Isolation ofa gene encoding a novel member of the nu-clear receptor superfamilyfrom the critical region of Usher syndrome type IIa at 1q41. Genomics 50:382–384, 1998.

[0855] 453.Greschik, H.; Wurtz, J.-M.; Sanglier, S.; Bourguet, W.; van Dorsselaer,A.; Moras, D.; Renaud, J.-P.: Structural and

functional evidencefor ligand-independent transcriptional activation by the estrogen-relatedreceptor 3. Molec. Cell 9: 303-313, 2002.

[0856]   454.Ding, H.; Descheemaeker, K.; Marynen, P.; Nelles, L.; Carvalho,T.; Carmo-Fonseca, M.; Collen, D.; Belayew, A.: Characterizationof a helicase-like transcription factor involved in the expressionof the human plasminogen activator inhibitor-1 gene. DNA Cell Biol. 15:429-442, 1996.

[0857]   455.Lin, Y.; Sheridan, P. L.; Jones, K. A.; Evans, G. A.: The HIP116SNF2/SWI2-related transcription factor gene (SNF2L3) is located onhuman chromosome 3q25.1-q26.1 Genomics 27: 381-382, 1995.

[0858]   456.Moinova, H. R.; Chen, W.-D.; Shen, L.; Smiraglia, D.; Olechnowicz,J.; Ravi, L.; Kasturi, L.; Myeroff, L.; Plass, C.; Parsons, R.; Minna,J.; Willson, J. K. V.; Green, S. B.; Issa, J.-P.; Markowitz, S. D.: HLTF gene silencing in human colon cancer. Proc. Nat. Acad. Sci. 99:4562-4567, 2002.

[0859]   457.Sheridan, P. L.; Schorpp, M.; Voz, M. L.; Jones, K. A.: Cloningof an SNF2/SWI2-related protein that binds specifically to the SPHmotifs of the SV40 enhancer and to the HIV-1 promoter. J. Biol. Chem. 270:4575-4587, 1995.

[0860]   458.Heard, D. J.; Norby, P. L.; Holloway, J.; Vissing, H.: Human ERR-gamma,a third member of the estrogen re-

ceptor-related receptor (ERR) subfamilyof orphan nuclear receptors: tissue-specific isoforms are expressedduring development in the adult. Molec. Endocr. 14: 382-392, 2000.

[0861] 459.Hong, H.; Yang, L.; Stallcup, M. R.: Hormone-independent transcriptionalactivation and coactivator binding by novel orphan nuclear receptorERR3. J. Biol. Chem. 274: 22618-22626, 1999.

[0862] 460.Schiebel, K.; Winkelmann, M.; Mertz, A.; Xu, X.; Page, D. C.; Weil,D.; Petit, C.; Rappold,, G. A.: Abnormal XY interchange between anovel isolated protein kinase gene, PRKY, and its homologue, PRKX,accounts for one third of all (Y+)XX males and (Y-)XY females. Hum.Molec. Genet. 6: 1985-1989, 1997.

[0863] 461.Bejjani, B. A.; Lewis, R. A.; Tomey, K. F.; Anderson, K. L.; Dueker,D. K.; Jabak, M.; Astle, W. F.; Otterud, B.; Leppert, M.; Lupski,J. R.: Mutations in CYP1B1, the gene for cytochrome P4501B1, arethe predominant cause of primary congenital glaucoma in Saudi Arabia. Am.J. Hum. Genet. 62: 325-333, 1998.

[0864] 462.Bejjani, B. A.; Stockton, D. W.; Lewis, R. A.; Tomey, K. F.; Dueker,D. K.; Jabak, M.; Astle, W. F.; Lupski, J. R.: Multiple CYP1B1 mutationsand incomplete penetrance in an

inbred population segregating primarycongenital glaucoma suggest frequent de novo events and a dominantmodifier locus. Hum. Molec. Genet. 9: 367-374, 2000.

[0865] 463.Konig, A.; Happle, R.; Fink-Puches, R.; Soyer, H. P.; Bornholdt,D.; Engel, H.; Grzeschik, K.-H.: A novel missense mutation of NSDHLin an unusual case of CHILD syndrome showing bilateral, almost symmetricinvolvement. J. Am. Acad. Derm. 46: 594-596, 2002.

[0866] 464.Labit-Le Bouteiller, C.; Jamme, M. F.; David, M.; Silve, S.; Lanau,C.; Dhers, C.; Picard, C.; Rahier, A.; Taton, M.; Loison, G.; Caput,D.; Ferrara, P.; Lupker, J.: Antiproliferative effects of SR31747Ain animal cell lines are mediated by inhibition of cholesterol biosynthesisat the sterol isomerase step. Europ. J. Biochem. 256: 342-349, 1998.

[0867] 465.Liu, X. Y.; Dangel, A. W.; Kelley, R. I.; Zhao, W.; Denny, P.;Botcherby, M.; Cattanach, B.; Peters, J.; Hunsicker, P. R.; Mallon,A.-M.; Strivens, M. A.; Bate, R.; Miller, W.; Rhodes, M.; Brown, S.D. M.; Herman, G. E.: The gene mutated in bare patches and striatedmice encodes a novel 3-beta-hydroxysteroid dehydrogenase. NatureGenet. 22: 182-187, 1999.

[0868] 466.Schindelhauer, D.; Hellebrand, H.; Grimm, L.; Bader, I.; Meitinger,T.; Wehnert, M.; Ross, M.; Meindl, A.: Long-

range map of a 3.5-Mbregion in Xp11.23-22 with a se-
quence-ready map from a 1.1-Mb gene-richinterval.
Genome Res. 6: 1056-1069, 1996.

[0869] 467.Silve, S.; Dupuy, P. H.; Labit-Lebouteiller, C.; Kaghad,
M.; Chalon,P.; Rahier, A.; Taton, M.; Lupker, J.; Shire, D.;
Loison, G.: Emopamil-bindingprotein, a mammalian pro-
tein that binds a series of structurally diverseneuroprotec-
tive agents, exhibits delta(8)-delta(7) sterol isomeraseac-
tivity in yeast. J. Biol. Chem. 271: 22434-22440, 1996.

[0870] 468.Traupe, H.; Muller, D.; Atherton, D.; Kalter, D. C.;
Cremers,F. P. M.; van Oost, B. A.; Ropers, H.-H.: Exclusion
mapping of theX-linked dominant chondrodysplasia
punctata/ichthyosis/cataract/shortstature (Happle) syn-
drome: possible involvement of an unstable pre-mutation.
Hum.Genet. 89: 659-665, 1992.

[0871] 469.Lankes, W.; Griesmacher, A.; Grunwald, J.; Schwartz-Al-
biez, R.;Keller, R.: A heparin-binding protein involved in
inhibition of smooth-musclecell proliferation. Biochem. J.
251: 831-842, 1988.

[0872] 470.Lankes, W. T.; Furthmayr, H.: Moesin: a member of
the protein4.1-talin-ezrin family of proteins. Proc. Nat.
Acad. Sci. 88: 8297-8301,1991.

[0873] 471.Shcherbina, A.; Bretscher, A.; Rosen, F. S.; Kenney, D.

M.; Remold-O'Donnell,E.: The cytoskeletal linker protein moesin: decreased levels in Wiskott-Aldrichsyndrome platelets and identification of a cleavage pathway in nor-malplatelets. Brit. J. Haemat. 106: 216-223, 1999.

[0874] 472.Wilgenbus, K. K.; Hsieh, C.-L.; Lankes, W. T.; Mila-tovich, A.;Francke, U.; Furthmayr, H.: Structure and local-ization on the X chromosomeof the gene coding for the human filopodial protein moesin (MSN). Genomics 19:326-333, 1994.

[0875] 473.Hanna, I. H.; Dawling, S.; Roodi, N.; Guengerich, F. P.; Parl,F. F.: Cytochrome P450 1B1 (CYP1B1) pharmacoge-netics: associationof polymorphisms with functional dif-ferences in estrogen hydroxylationactivity. Cancer Res. 60: 3440-3444, 2000.

[0876] 474.Plasilova, M.; Stoilov, I.; Sarfarazi, M.; Kadasi, L.; Fer-akova,E.; Ferak, V.: Identification of a single ancestral CYP1B1 mutationin Slovak Gypsies (Roms) affected with primary congenital glaucoma. J.Med. Genet. 36: 290-294, 1999.

[0877] 475.Schwartzman, M. L.; Balazy, M.; Masferrer, J.; Abra-ham, N. G.;McGiff, J. C.; Murphy, R. C.: 12(R)-hydroxyicosatetraenoic acid:a cytochrome P450-dependent arachidonate metabolite that inhibit-

sNa+,K+-ATPase in the cornea. Proc. Nat. Acad. Sci. 84: 8125-8129,1987.

[0878] 476.Stoilov, I.; Akarsu, A. N.; Alozie, I.; Child, A.; Barsoum-Homsy,M.; Turacli, M. E.; Or, M.; Lewis, R. A.; Ozdemir, N.; Brice, G.;Aktan, S. G.; Chevrette, L.; Coca-Prados, M.; Sarfarazi, M.: Sequenceanalysis and homology modeling suggest that primary congenital glaucomaon 2p21 results from mutations disrupting either the hinge regionor the conserved core structures of cytochrome P4501B1. Am. J. Hum.Genet. 62: 573-584, 1998.

[0879] 477.Stoilov, I.; Akarsu, A. N.; Sarfarazi, M.: Identification of threedifferent truncating mutations in cytochrome P4501B1 (CYP1B1) as theprincipal cause of primary congenital glaucoma (buphthalmos) in familieslinked to the GLC3A locus on chromosome 2p21. Hum. Molec. Genet. 6:641-647, 1997.

[0880] 478.Sutter, T. R.; Tang, Y. M.; Hayes, C. L.; Wo, Y.-Y. P.; Jabs, E.W.; Li, X.; Yin, H.; Cody, C. W.; Greenlee, W. F.: Complete cDNAsequence of a human dioxin-inducible mRNA identifies a new gene subfamilyof cytochrome P450 that maps to chromosome 2. J. Biol. Chem. 269:13092-13099, 1994.

[0881] 479.Tang, Y. M.; Wo, Y.-Y. P.; Stewart, J.; Hawkins, A. L.;

Griffin,C. A.; Sutter, T. R.; Greenlee, W. F.: Isolation and characterizationof the human cytochrome P450 CYP1B1 gene. J. Biol. Chem. 271: 28324–28330,1996.

[0882] 480.Vincent, A.; Billingsley, G.; Priston, M.; Williams-Lyn, D.; Sutherland,J.; Glaser, T.; Oliver, E.; Walter, M. A.; Heathcote, G.; Levin, A.;Heon, E.: Phenotypic heterogeneity of CYP1B1: mutations in a patientwith Peters' anomaly. J. Med. Genet. 38: 324–326, 2001.

[0883] 481.Wu, Q.; Zhang, T.; Cheng, J.-F.; Kim, Y.; Grimwood, J.; Schmutz,J.; Dickson, M.; Noonan, J. P.; Zhang, M. Q.; Myers, R. M.; Maniatis,T.: Comparative DNA sequence analysis of mouse and human protocadheringene clusters. Genome Res. 11: 389–404, 2001.

[0884] 482.Field, S. J.; Tsai, F.-Y.; Kuo, F.; Zubiaga, A. M.; Kaelin, W.G., Jr.; Livingston, D. M.; Orkin, S. H.; Greenberg, M. E.: E2F-1functions in mice to promote apoptosis and suppress proliferation. Cell 85:549–561, 1996.

[0885] 483.Helin, K.; Lees, J. A.; Vidal, M.; Dyson, N.; Harlow, E.; Fattaey,A.: A cDNA encoding a pRB-binding protein with properties of thetranscription factor E2F. Cell 70: 337–350, 1992.

[0886] 484.Irwin, M.; Marin, M. C.; Phillips, A. C.; Seelan, R. S.; Smith,D. I.; Liu, W.; Flores, E. R.; Tsai, K. Y.; Jacks, T.;

Vousden, K.H.; Kaelin, W. G., Jr.: Role for the p53 homo-
logue p73 in E2F-1-inducedapoptosis. Nature 407:
645-648, 2000.

[0887] 485.Jacks, T.; Fazeli, A.; Schmitt, E. M.; Bronson, R. T.;
Goodell,M. A.; Weinberg, R. A.: Effects of an Rb mutation
in the mouse. Nature 359:295-300, 1992.

[0888] 486.Lees, J. A.; Saito, M.; Valentine, M.; Look, T.; Harlow,
E.; Dyson,N.; Helin, K.: The retinoblastoma protein binds
to a family of E2Ftranscription factors. Molec. Cell. Biol.
13: 7813-7825, 1993.

[0889] 487.Leone, G.; Sears, R.; Huang, E.; Rempel, R.; Nuckolls,
F.; Park,C.-H.; Giangrande, P.; Wu, L.; Saavedra, H. I.;
Field, S. J.; Thompson,M. A.; Yang, H.; Fujiwara, Y.; Green-
berg, M. E.; Orkin, S.; Smith,C.; Nevins, J. R.: Myc requires
distinct E2F activities to induceS phase and apoptosis.
Molec. Cell 8: 105-113, 2001.

[0890] 488.Lissy, N. A.; Davis, P. K.; Irwin, M.; Kaelin, W. G.;
Dowdy, S.F.: A common E2F-1 and p73 pathway mediates
cell death induced byTCR activation. Nature 407:
642-645, 2000.

[0891] 489.Neuman, E.; Sellers, W. R.; McNeil, J. A.; Lawrence, J.
B.; Kaelin,W. G., Jr.: Structure and partial genomic se-
quence of the human E2F1gene. Gene 173: 163-169,

1996.

[0892] 490.Nevins, J. R.: The Rb/E2F pathway and cancer. Hum. Molec. Genet. 10:699–703, 2001.

[0893] 491.Nevins, J. R.: E2F: a link between the Rb tumor suppressor proteinand viral oncoproteins. Science 258: 424–429, 1992.

[0894] 492.Ohtani, K.; DeGregori, J.; Nevins, J. R.: Regulation of the cyclinE gene by transcription factor E2F1. Proc. Nat. Acad. Sci. 92: 12146–12150,1995.

[0895] 493.Arden, K. C.; Boutin, J.-M.; Djiane, J.; Kelly, P. A.; Cavenee,W. K.: The receptors for prolactin and growth hormone are localizedin the same region of human chromosome 5. Cytogenet. Cell Genet. 53:161–165, 1990.

[0896] 494.Arden, K. C.; Cavenee, W. K.; Boutin, J.-M.; Kelly, P. A.: Thegenes encoding the receptors for prolactin and growth hormone mapto human chromosome 5. (Abstract) Am. J. Hum. Genet. 45 (suppl.):A129 only, 1989.

[0897] 495.Boutin, J.-M.; Edery, M.; Shirota, M.; Jolicoeur, C.; Lesueur,L.; Ali, S.; Gould, D.; Djiane, J.; Kelly, P. A.: Identificationof a cDNA encoding a long form of prolactin receptor in human hepatomaand breast cancer cells. Molec. Endocr. 3: 1455–1461, 1989.

[0898] 496.Cunningham, B. C.; Bass, S.; Fuh, G.; Wells, J. A.: Zinc

mediationof the binding of human growth hormone to the human prolactin receptor. Science 250:1709–1712, 1990.

[0899] 497.Glasow, A.; Horn, L.-C.; Taymans, S. E.; Stratakis, C. A.; Kelly,P. A.; Kohler, U.; Gillespie, J.; Vonderhaar, B. K.; Bornstein, S.R.: Mutational analysis of the PRL receptor gene in human breasttumors with differential PRL receptor protein expression. J. Clin.Endocr. Metab. 86: 3826–3832, 2001.

[0900] 498.Hu, Z.-Z.; Zhuang, L.; Meng, J.; Leondires, M.; Dufau, M. L.:The human prolactin receptor gene structure and alternative promoterutilization: the generic promoter hPIII and a novel human promoterhP(N). J. Clin. Endocr. Metab. 84: 1153–1156, 1999.

[0901] 499.Ormandy, C. J.; Camus, A.; Barra, J.; Damotte, D.; Lucas, B.; Buteau,H.; Edery, M.; Brousse, N.; Babinet, C.; Binart, N.; Kelly, P. A.: Null mutation of the prolactin receptor gene produces multiple reproductivedefects in the mouse. Genes Dev. 11: 167–178, 1997.

[0902] 500.Perrot-Applanat, M.; Gualillo, O.; Pezet, A.; Vincent, V.; Edery,M.; Kelly, P. A.: Dominant negative and cooperative effects of mutantforms of prolactin receptor. Molec. Endocr. 11: 1020–1032, 1997.

[0903] 501.Brenneman, M. A.; Wagener, B. M.; Miller, C. A.; Allen,

C.; Nickoloff,J. A.: XRCC3 controls the fidelity of homologous recombination: rolesfor XRCC3 in late stages of recombination. Molec. Cell 10: 387-395,2002.

[0904] 502.Liu, N.; Lamerdin, J. E.; Tebbs, R. S.; Schild, D.; Tucker, J.D.; Shen, M. R.; Brookman, K. W.; Siciliano, M. J.; Walter, C. A.;Fan, W.; Narayana, L. S.; Zhou, Z.-Q.; Adamson, A. W.; Sorensen, K.J.; Chen, D. J.; Jones, N. J.; Thompson, L. H.: XRCC2 and XRCC3,new human Rad51-family members, promote chromosome stability and protectagainst DNA cross-links and other damages. Molec. Cell 1: 783-793,1998.

[0905] 503.Tebbs, R. S.; Zhao, Y.; Tucker, J. D.; Scheerer, J. B.; Siciliano,M. J.; Hwang, M.; Liu, N.; Legerski, R. J.; Thompson, L. H.: Correctionof chromosomal instability and sensitivity to diverse mutagens bya cloned cDNA of the XRCC3 DNA repair gene. Proc. Nat. Acad. Sci. 92:6354-6358, 1995.

[0906] 504.Winsey, S. L.; Haldar, N. A.; Marsh, H. P.; Bunce, M.; Marshall,S. E.; Harris, A. L.; Wojnarowska, F.; Welsh, K. I.: A variant withinthe DNA repair gene XRCC3 is associated with the development of melanomaskin cancer. Cancer Res. 60: 5612-5616, 2000.

[0907] 505.Fischle, W.; Dequiedt, F.; Hendzel, M. J.; Guenther, M. G.; Lazar,M. A.; Voelter, W.; Verdin, E.: Enzymatic activity

associated withclass II HDACs is dependent on a multipro-
tein complex containing HDAC3and SMRT/N-CoR. Molec.
Cell 9: 45-57, 2002.

[0908] 506.Patil, N.; Cox, D. R.; Bhat, D.; Faham, M.; Myers, R. M.;
Peterson,A. S.: A potassium channel mutation in weaver
mice implicates membraneexcitability in granule cell dif-
ferentiation. Nature Genet. 11:126-129, 1995.

[0909] 507.Al-Chalabi, A.; Andersen, P. M.; Nilsson, P.; Chioza,
B.; Andersson,J. L.; Russ, C.; Shaw, C. E.; Powell, J. F.;
Leigh, P. N.: Deletionsof the heavy neurofilament subunit
tail in amyotrophic lateral sclerosis. Hum.Molec. Genet. 8:
157-164, 1999.

[0910] 508.Collard, J.-F.; Cote, F.; Julien, J.-P.: Defective axonal
transportin a transgenic mouse model of amyotrophic lat-
eral sclerosis. Nature 375:61-64, 1995.

[0911] 509.Figlewicz, D. A.; Krizus, A.; Martinoli, M. G.;
Meininger, V.;Dib, M.; Rouleau, G. A.; Julien, J.-P.: Variants
of the heavy neurofilamentsubunit are associated with the
development of amyotrophic lateralsclerosis. Hum. Molec.
Genet. 3: 1757-1761, 1994.

[0912] 510.Lees, J. F.; Shneidman, P. S.; Skuntz, S. F.; Carden, M.
J.; Lazzarini,R. A.: The structure and organization of the
human heavy neurofilamentsubunit (NF-H) and the gene

encoding it. EMBO J. 7: 1947–1955, 1988.

[0913] 511.Mattei, M.-G.; Dautigny, A.; Pham-Dinh, D.; Passage,
E.; Mattei,J.-F.; Jolles, P.: The gene encoding the large hu-
man neurofilamentsubunit (NF-H) maps to the q121-q131
region on human chromosome 22. Hum.Genet. 80:
293–295, 1988.

[0914] 512.Rooke, K.; Figlewicz, D. A.; Han, F.; Rouleau, G. A.:
Analysisof the KSP repeat of the neurofilament heavy sub-
unit in familial amyotrophiclateral sclerosis. Neurology 46:
789–790, 1996.

[0915] 513.Rouleau, G. A.; Merel, P.; Lutchman, M.; Sanson, M.;
Zucman, J.;Marineau, C.; Hoang-Xuan, K.; Demczuk, S.;
Desmaze, C.; Plougastel,B.; Pulst, S. M.; Lenoir, G.; Bi-
jlsma, E.; Fashold, R.; Dumanski,J.; de Jong, P.; Parry, D.;
Eldrige, R.; Aurias, A.; Delattre, O.;Thomas, G.: Alteration
in a new gene encoding a putative membrane-or-
ganizingprotein causes neuro-fibromatosis type 2. Nature
363: 515–521, 1993.

[0916] 514.Tomkins, J.; Usher, P.; Slade, J. Y.; Ince, P. G.; Curtis,
A.;Bushby, K.; Shaw, P. J.: Novel insertion in the KSP region
of theneurofilament heavy gene in amyotrophic lateral
sclerosis. Neuroreport 9:3967–3970, 1998.

[0917] 515.Vechio, J. D.; Bruijn, L. I.; Xu, Z.; Brown, R. H., Jr.;

Cleveland,D. W.: Sequence variants in human neurofilament proteins: absenceof linkage to familial amyotrophic lateral sclerosis. Ann. Neurol. 40:603-610, 1996.

[0918] 516.Watson, C. J.; Gaunt, L.; Evans, G.; Patel, K.; Harris, R.; Strachan,T.: A disease-associated germline deletion maps the type 2 neurofibromatosis(NF2) gene between the Ewing sarcoma region and the leukaemia inhibitoryfactor locus. Hum. Molec. Genet. 2: 701-704, 1993.

[0919] 517.Bongarzone, I.; Vigano, E.; Alberti, L.; Borrello, M. G.; Pasini,B.; Greco, A.; Mondellini, P.; Smith, D. P.; Ponder, B. A. J.; Romeo,G.; Pierotti, M. A.: Full activation of MEN2B mutant RET by an additionalMEN2A mutation or by ligand GDNF stimulation. Oncogene 16: 2295-2301,1998.

[0920] 518.Carlson, K. M.; Bracamontes, J.; Jackson, C. E.; Clark, R.; Lacroix,A.; Wells, S. A., Jr.; Goodfellow, P. J.: Parent-of-origin effectsin multiple endocrine neoplasia type 2B. Am. J. Hum. Genet. 55:1076-1082, 1994.

[0921] 519.Carlson, K. M.; Dou, S.; Chi, D.; Scavarda, N.; Toshima, K.; Jackson,C. E.; Wells, S. A., Jr.; Goodfellow, P. J.; Donis-Keller, H.: Singlemissense mutation in the tyrosine kinase catalytic domain of the RETprotooncogene is associated with multiple endocrine neoplasia type2B. Proc. Nat. Acad. Sci. 91: 1579-1583, 1994.

[0922] 520.Mulligan, L. M.; Eng, C.; Healey, C. S.; Clayton, D.; Kwok, J.B. J.; Gardner, E.; Ponder, M. A.; Frilling, A.; Jackson, C. E.; Lehnert,H.; Neumann, H. P. H.; Thibodeau, S. N.; Ponder, B. A. J.: Specificmutations of the RET proto-oncogene are related to disease phenotypein MEN 2A and FMTC. Nature Genet. 6: 70-74, 1994.

[0923] 521.Grozinger, C. M.; Hassig, C. A.; Schreiber, S. L.: Three proteinsdefine a class of human histone deacetylases related to yeast Hda1p. Proc.Nat. Acad. Sci. 96: 4868-4873, 1999.

[0924] 522.Sturm, R. A.; Eyre, H. J.; Baker, E.; Sutherland, G. R.: The humanOTF1 locus which overlaps the CD3Z gene is located at 1q22-q23. Cytogenet.Cell Genet. 68: 231-232, 1995.

[0925] 523.Klink, A.; Schiebel, K.; Winkelmann, M.; Rao, E.; Hors-themke, B.;Ludecke, H.-J.; Claussen, U.; Scherer, G.; Rappold, G.: The humanprotein kinase gene PKX1 on Xp22.3 displays Xp/Yp homology and isa site of chromosomal instability. Hum. Molec. Genet. 4: 869-878,1995.

[0926] 524.Schiebel, K.; Mertz, A.; Winkelmann, B.; Glaser, B.; Schempp, W.;Rappold, G.: FISH localization of the human Y-homolog of proteinkinase PRKX (PRKY) to Yp11.2 and two pseudogenes to 15q26 and Xq12-q13. Cytogenet.Cell

Genet. 76: 49-52, 1997.

[0927] 525.Lee, S. M. Y.; Tsui, S. K. W.; Chan, K. K.; Garcia-Barcelo, M.;Waye, M. M. Y.; Fung, K. P.; Liew, C. C.; Lee, C. Y.: Chromosomalmapping, tissue distribution and cDNA sequence of four-and-a-halfLIM domain protein 1 (FHL1). Gene 216: 163-170, 1998.

[0928] 526.Morgan, M. J.; Madgwick, A. J.; Charleston, B.; Pell, J. M.; Loughna,P. T.: The developmental regulation of a novel muscle LIM-protein. Biochem.Biophys. Res. Commun. 212: 840-846, 1995.

[0929] 527.Morgan, M. J.; Madgwick, A. J. A.: Slim defines a novel familyof LIM-proteins expressed in skeletal muscle. Biochem. Biophys. Res.Commun. 225: 632-638, 1996.

[0930] 528.Bowcock, A. M.; Kidd, J. R.; Lathrop, G. M.; Daneshvar, L.; May,L. T.; Ray, A.; Sehgal, P. B.; Kidd, K. K.; Cavalli-Sforza, L. L.: The human 'interferon-beta-2/hepatocyte stimulating factor/interleukin-6'gene: DNA polymorphism studies and localization to chromosome 7p21. Genomics 3:8-16, 1988.

[0931] 529.Chen, Y.; Ferguson-Smith, A. C.; Newman, M. S.; May, L. T.; Sehgal,P. B.; Ruddle, F. H.: Regional localization of the human beta 2-interferongene. (Abstract) Am. J. Hum. Genet. 41: A161, 1987.

[0932] 530.Chow, D.; He, X.; Snow, A. L.; Rose-John, S.; Garcia, K. C.: Structureof an extracellular gp130 cytokine receptor signaling complex. Science 291:2150-2155, 2001.

[0933] 531.Chung, U.; Tanaka, Y.; Fujita, T.: Association of inter-leukin-6and hypoaldosteronism in patients with cancer. (Letter) New Eng.J. Med. 334: 473, 1996.

[0934] 532.Cressman, D. E.; Greenbaum, L. E.; DeAngelis, R. A.; Ciliberto,G.; Furth, E. E.; Poli, V.; Taub, R.: Liver failure and defectivehepatocyte regeneration in interleukin-6-deficient mice. Science 274:1379-1382, 1996.

[0935] 533.De Benedetti, F.; Alonzi, T.; Moretta, A.; Lazzaro, D.; Costa,P.; Poli, V.; Martini, A.; Ciliberto, G.; Fattori, E.: In-terleukin6 causes growth impairment in transgenic mice through a decrease ininsulin-like growth factor-I. J. Clin. Invest. 99: 643-650, 1997.

[0936] 534.Ferguson-Smith, A. C.; Chen, Y.-F.; Newman, M. S.; May, L. T.;Sehgal, P. B.; Ruddle, F. H.: Regional localization of the interferonbeta-2/B-cell stimulatory factor 2/hepatocyte stimulating factor geneto human chromo-some 7p15-p21. Genomics 2: 203-208, 1988.

[0937] 535.Fernandez-Real, J.-M.; Broch, M.; Vendrell, J.; Richart, C.; Ricart,W.: Interleukin-6 gene polymorphism and lipid abnormalities in healthysubjects. J. Clin. Endocr. Metab.

85: 1334–1339, 2000.

[0938]   536.Fishman, D.; Faulds, G.; Jeffery, R.; Mohamed-Ali, V.; Yudkin,J. S.; Humphries, S.; Woo, P.: The effect of novel polymorphismsin the interleukin-6 (IL-6) gene on IL-6 transcription and plasmaIL-6 levels, and an association with systemic-onset juvenile chronicarthritis. J. Clin. Invest. 102: 1369–1376, 1998.

[0939]   537.Foster, C. B.; Lehrnbecher, T.; Samuels, S.; Stein, S.; Mol, F.;Metcalf, J. A.; Wyvill, K.; Steinberg, S. M.; Kovacs, J.; Blauvelt,A.; Yarchoan, R.; Chanock, S. J.: An IL6 promoter polymorphism isassociated with a lifetime risk of development of Kaposi sarcoma inmen infected with human immunodeficiency virus. Blood 96: 2562–2567,2000.

[0940]   538.Funatsu, H.; Yamashita, H.; Noma, H.; Mimura, T.; Yamashita, T.;Hori, S.: Increased levels of vascular endothelial growth factorand interleukin-6 in the aqueous humor of diabetics with macular edema. Am.J. Ophthal. 133: 70–77, 2002.

[0941]   539.Hirano, T.; Yasukawa, K.; Harada, H.; Taga, T.; Watanabe, Y.;Matsuda, T.; Kashiwamura, S.; Nakajima, K.; Koyama, K.; Iwamatsu,A.; Tsunasawa, S.; Sakiyama, F.; Matsui, H.; Takahara, Y.; Taniguchi,T.; Kishimoto, T.: Complementary DNA for a novel human interleukin(BSF-2)

that induces B lymphocytes to produce immunoglobulin. Nature 324:73-76, 1986.

[0942] 540.Kawano, M.; Hirano, T.; Matsuda, T.; Taga, T.; Horii, Y.; Iwato,K.; Asaoku, H.; Tang, B.; Tanabe, O.; Tanaka, H.; Kuramoto, A.; Kishimoto,T.: Autocrine generation and requirement of BSF-2/IL-6 for humanmultiple myelomas. Nature 332: 83-85, 1988.

[0943] 541.Kovalchuk, A. L.; Kim, J. S.; Park, S. S.; Coleman, A. E.; Ward,J. M.; Morse, H. C, III; Kishimoto, T.; Potter, M.; Janz, S.: IL-6transgenic mouse model for extraosseous plasmacytoma. Proc. Nat.Acad. Sci. 99: 1509-1514, 2002.

[0944] 542.May, L. T.; Ghrayeb, J.; Santhanam, U.; Tatter, S. B.; Sthoeger,Z.; Helfgott, D. C.; Chiorazzi, N.; Grieninger, G.; Sehgal, P. B.: Synthesis and secretion of multiple forms of beta-2-interferon/B-celldifferentiation factor 2/hepatocyte-stimulating factor by human fibroblastsand monocytes. J. Biol. Chem. 263: 7760-7766, 1988.

[0945] 543.Ota, N.; Hunt, S. C.; Nakajima, T.; Suzuki, T.; Hosoi, T.; Orimo,H.; Shirai, Y.; Emi, M.: Linkage of interleukin 6 locus to humanosteopenia by sibling pair analysis. Hum. Genet. 105: 253-257, 1999.

[0946] 544.Ota, N.; Nakajima, T.; Nakazawa, I.; Suzuki, T.; Hosoi, T.; Orimo,H.; Inoue, S.; Shirai, Y.; Emi, M.: A nucleotide

variant in the promoterregion of the interleukin-6 gene associated with decreased bone mineraldensity. J. Hum. Genet. 46: 267-272, 2001.

[0947] 545.Redwine, L.; Hauger, R. L.; Gillin, J. C.; Irwin, M.: Effectsof sleep and sleep deprivation on interleukin-6, growth hormone, cortisol,and melatonin levels in humans. J. Clin. Endocr. Metab. 85: 3597-3603,2000.

[0948] 546.Roodman, G. D.; Kurihara, N.; Ohsaki, Y.; Kukita, A.; Hosking,D.; Demulder, A.; Smith, J. F.; Singer, F. R.: Interleukin 6: a potentialautocrine/paracrine factor in Paget's disease of bone. J. Clin. Invest. 89:46-52, 1992.

[0949] 547.Rooney, M.; David, J.; Symons, J.; Di Giovine, F.; Varsani, H.;Woo, P.: Inflammatory cytokine responses in juvenile chronic arthritis. Brit.J. Rheum. 34: 454-460, 1995.

[0950] 548.Santhanam, U.; Ray, A.; Sehgal, P. B.: Repression of the interleukin6 gene promoter by p53 and the retinoblastoma susceptibility geneproduct. Proc. Nat. Acad. Sci. 88: 7605-7609, 1991.

[0951] 549.Scheidt-Nave, C.; Bismar, H.; Leidig-Bruckner, G.; Woitge, H.;Seibel, M. J.; Ziegler, R.; Pfeilschifter, J.: Serum interleukin6 is a major predictor of bone loss in women specific to the firstdecade past menopause. J. Clin. En-

docr. Metab. 86: 2032-2042, 2001.

[0952] 550.Sehgal, P. B.; May, L. T.; Tamm, I.; Vilcek, J.: Human beta-2interferon and B-cell differentiation factor BSF-2 are identical. Science 235:731-732, 1987.

[0953] 551.Sehgal, P. B.; Walther, Z.; Tamm, I.: Rapid enhancement of beta(2)-interferon/B-celldifferentiation factor BSF-2 gene expression in human fibroblastsby diacylglycerols and the calcium ionophore A23187. Proc. Nat. Acad.Sci. 84: 3663-3667, 1987.

[0954] 552.Sehgal, P. B.; Zilberstein, A.; Ruggieri, R.-M.; May, L. T.; Ferguson-Smith,A.; Slate, D. L.; Revel, M.; Ruddle, F. H.: Human chromosome 7 carriesthe beta-2 interferon gene. Proc. Nat. Acad. Sci. 83: 5219-5222,1986.

[0955] 553.Berube, D.; Simard, J.; Sandberg, M.; Grzeschik, K.-H.; Gagne,R.; Hansson, V.; Jahnsen, T.: Assignment of the gene encoding thecatalytic subunit C(beta) of cAMP-dependent protein kinase to thep36 band on chromosome 1. (Abstract) Cytogenet. Cell Genet. 58:1850 only, 1991.

[0956] 554.Sutherland, G. R.; Baker, E.; Callen, D. F.; Hyland, V. J.; Wong,G.; Clark, S.; Jones, S. S.; Eglinton, L. K.; Shannon, M. F.; Lopez,A. F.; Vadas, M. A.: Interleukin 4 is at 5q31 and interleukin 6 isat 7p15. Hum. Genet. 79: 335-337, 1988.

[0957] 555.Symmons, D. P.; Jones, M.; Osborne, J.; Sills, J.; Southwood,T. R.; Woo, P.: Pediatric rheumatology in the United Kingdom: datafrom the British Pediatric Rheumatology Group National DiagnosticRegister. J. Rheum. 23: 1975-1980, 1996.

[0958] 556.Tosato, G.; Seamon, K. B.; Goldman, N. D.; Sehgal, P. B.; May,L. T.; Washington, G. C.; Jones, K. D.; Pike, S. E.: Monocyte-derivedhuman B-cell growth factor identified as interferon-beta-2 (BSF-2,IL-6). Science 239: 502-504, 1988.

[0959] 557.Villuendas, G.; San Millan, J. L.; Sancho, J. and Esco-bar-Morreale,H. F.: The -597 G-A and -174 G-C poly-morphisms in the promoter ofthe IL-6 gene are associated with hyperandrogenism. J. Clin. Endocr.Metab. 87: 1134-1141, 2002.

[0960] 558.Zilberstein, A.; Ruggieri, R.; Korn, J. H.; Revel, M.: Structureand expression of cDNA and genes for human interferon-beta-2, a distinctspecies inducible by growth-stimulatory cytokines. EMBO J. 5: 2529-2537,1986.

[0961] 559.Diaz, M. O.; Le Beau, M. M.; Pitha, P.; Rowley, J. D.: Interferonand c-ets-1 genes in the translocation (9;11)(p22;q23) in human acutemonocytic leukemia. Science 231: 265-267, 1986.

[0962] 560.Ohlsson, M.; Feder, J.; Cavalli-Sforza, L. L.; von Gabain, A.: Close linkage of alpha and beta interferons and infrequent duplicationof beta interferon in humans. Proc. Nat. Acad. Sci. 82: 4473-4476,1985.

[0963] 561.Owerbach, D.; Rutter, W. J.; Shows, T. B.; Gray, P.; Goeddel,D. V.; Lawn, R. M.: Leukocyte and fibroblast interferon genes arelocated on human chromosome 9. Proc. Nat. Acad. Sci. 78: 3123-3127,1981.

[0964] 562.Siegal, F. P.; Kadowaki, N.; Shodell, M.; Fitzgerald-Bocarsly,P. A.; Shah, K.; Ho, S.; Antonenko, S.; Liu, Y.-J.: The nature ofthe principal type 1 interferon-producing cells in human blood. Science 284:1835-1837, 1999.

[0965] 563.Kramer, F.; White, K.; Pauleikhoff, D.; Gehrig, A.; Passmore,L.; Rivera, A.; Rudolph, G.; Kellner, U.; Andrassi, M.; Lorenz, B.;Rohrschneider, K.; Blankenagel, A.; Jurklies, B.; Schilling, H.; Schutt,F.; Holz, F. G.; Weber, B. H. F.: Mutations in the VMD2 gene areassociated with juvenile-onset vitelliform macular dystrophy (Bestdisease) and adult vitelliform macular dystrophy but not age-relatedmacular degeneration. Europ. J. Hum. Genet. 8: 286-292, 2000.

[0966] 564.Krill, A. E.; Morse, P. A.; Potts, A. M.; Klien, B. A.: Hereditaryvitelliruptive macular degeneration. Am. J. Ophthal. 61: 1405-1415,1966.

[0967] 565.Maloney, W. F.; Robertson, D. M.; Miller, S. A.: Hereditary vitelliformmacular degeneration--variable fundus findings within a single pedigree. Arch.Ophthal. 95: 979-983, 1977.

[0968] 566.Mansergh, F. C.; Kenna, P. F.; Rudolph, G.; Meitinger, T.; Farrar,G. J.; Kumar-Singh, R.; Scorer, J.; Hally, A. M.; Mynett-Johnson,L.; Humphries, M. M.; Kiang, S.; Humphries, P.: Evidence for geneticheterogeneity in Best's vitelliform macular dystrophy. J. Med. Genet. 32:855-858, 1995.

[0969] 567.Marmorstein, A. D.; Marmorstein, L. Y.; Rayborn, M.; Wang, X.;Hollyfield, J. G.; Petrukhin, K.: Bestrophin, the product of theBest vitelliform macular dystrophy gene (VMD2), localizes to the basolateralplasma membrane of the retinal pigment epithelium. Proc. Nat. Acad.Sci. 97: 12758-12763, 2000.

[0970] 568.Marquardt, A.; Stohr, H.; Passmore, L. A.; Kramer, F.; Rivera,A.; Weber, B. H. F.: Mutations in a novel gene, VMD2, encoding aprotein of unknown properties cause juvenile-onset vitelliform maculardystrophy (Best's disease). Hum. Molec. Genet. 7: 1517-1525, 1998.

[0971] 569.Nichols, B. E.; Bascom, R.; Litt, M.; McInnes, R.; Sheffield,V. C.; Stone, E. M.: Refining the locus for Best

vitelliform maculardystrophy and mutation analysis of the candidate gene ROM1. Am. J.Hum. Genet. 54: 95-103, 1994.

[0972] 570.Nordstrom, S.: Epidemiological studies of hereditary maculardegeneration (Best's disease) in Swedish and Swedish-American populations.In:Eriksson, A. W.; Forsius, H. R.; Nevanlinna, H. R.; Workman, P. L.;Norio, R. K.: Population Structure and Genetic Disorders. New York:Academic Press (pub.) 1980. Pp. 431-443.

[0973] 571.Nordstrom, S.: Personal Communication. Umea, Sweden 1978.

[0974] 572.Nordstrom, S.; Thorburn, W.: Dominantly inherited macular degeneration(Best's disease) in a homozygous father with 11 children. Clin. Genet. 18:211-216, 1980.

[0975] 573.O'Gorman, S.; Flaherty, W. A.; Fishman, G. A.; Berson, E. L.:Histopathologic findings in Best's vitelliform macular dystrophy. Arch.Ophthal. 106: 1261-1268, 1988.

[0976] 574.Petrukhin, K.; Koisti, M. J.; Bakall, B.; Li, W.; Xie, G.; Marknell,T.; Sandgren, O.; Forsman, K.; Holmgren, G.; Andreasson, S.; Vujic,M.; Bergen, A. A. B.; McGarty-Dugan, V.; Figueroa, D.; Austin, C.P.; Metzker, M. L.; Caskey, C. T.; Wadelius, C.: Identification ofthe gene responsible for Best macular dystrophy. Nature Genet. 19:241-247, 1998.

[0977] 575.Rivas, F.; Ruiz, C.; Rivera, H.; Moller, M.; Serrano-Lucas, J.I.; Cantu, J. M.: De novo del(6)(q25) associated with macular degeneration. Ann.Genet. 29: 42-44, 1986.

[0978] 576.Rosas, F. E.: Maculopatia hereditaria viteliforme de Best. Ann.Soc. Mex. Oft. 50: 157-171, 1976.

[0979] 577.Sorsby, A.; Savory, M.; Davey, J. B.; Fraser, R. J. L.: Macularcysts: a dominantly inherited affection with a progressive course. Brit.J. Ophthal. 40: 144-158, 1956.

[0980] 578.Stohr, H.; Marquardt, A.; Rivera, A.; Cooper, P. R.; Nowak, N.J.; Shows, T. B.; Gerhard, D. S.; Weber, B. H. F.: A gene map ofthe Best's vitelliform macular dystrophy region in chromosome 11q12-q13.1. GenomeRes. 8: 48-56, 1998.

[0981] 579.Stone, E. M.; Nichols, B. E.; Streb, L. M.; Kimura, A. E.; Sheffield,V. C.: Genetic linkage of vitelliform macular degeneration (Best'sdisease) to chromosome 11q13. Nature Genet. 1: 246-250, 1992.

[0982] 580.Sun, H.; Tsunenari, T.; Yau, K.-W.; Nathans, J.: The vitelliformmacular dystrophy protein defines a new family of chloride channels. Proc.Nat. Acad. Sci. 99: 4008-4013, 2002.

[0983] 581.Vail, D.; Shoch, D.: Hereditary degeneration of the macula. II.Follow-up report and histopathologic study.

Trans. Am. Ophthal. Soc. 63:51–63, 1965.

[0984] 582.Vossius, A.: Ueber die Bestsche familiaere Maculade-generation. Arch.Ophthal. 105: 1050–1059, 1921.

[0985] 583.Weber, B. H. F.; Walker, D.; Muller, B.: Molecular evidence fornon-penetrance in Best's disease. J. Med. Genet. 31: 388–392, 1994.

[0986] 584.Weber, B. H. F.; Walker, D.; Muller, B.; Mar, L.: Best's vitelliformdystrophy (VMD2) maps between D11S903 and PYGM: no evidence for locusheterogeneity. Genomics 20: 267–274, 1994.

[0987] 585.White, K.; Marquardt, A.; Weber, B. H. F.: VMD2 mutations invitelliform macular dystrophy (Best disease) and other maculopathies. Hum.Mutat. 15: 301–308, 2000.

[0988] 586.Yoder, F. E.; Cross, H. E.; Chase, G. A.; Fine, S. L.; Freidhoff,L.; Machan, C. H.; Bias, W. B.: Linkage studies of Best's maculardystrophy. Clin. Genet. 34: 26–30, 1988.

[0989] 587.Farndon, J. R.; Leight, G. S.; Dilley, W. G.; Baylin, S. B.; Smallridge,R. C.; Harrison, T. S.; Wells, S. A., Jr.: Familial medullary thyroidcarcinoma without associated endocrinopathies: a distinct clinicalentity. Brit. J. Surg. 73: 278–281, 1986.

[0990] 588.Allen, G.; Fantes, K. H.: A family of structural genes for humanlymphoblastoid (leucocyte-type) interferon. Na-

ture 287: 408–411,1980.

[0991] 589.Diaz, M. O.; Bohlander, S.; Allen, G.: Nomenclature of the humaninterferon genes. J. Interferon Cytokine Res. 16: 179–180, 1996.

[0992] 590.Diaz, M. O.; Pomykala, H. M.; Bohlander, S. K.; Maltepe, E.; Malik,K.; Brownstein, B.; Olopade, O. I.: Structure of the human type-Iinterferon gene cluster determined from a YAC clone contig. Genomics 22:540–552, 1994.

[0993] 591.Douglas, R. M.; Moore, B. W.; Miles, H. B.; Davies, L. M.; Graham,N. M. H.; Ryan, P.; Worswick, D. A.; Albrecht, J. K.: Prophylacticefficacy of intranasal alpha-2-interferon against rhinovirus infectionsin the family setting. New Eng. J. Med. 314: 65–70, 1986.

[0994] 592.Edge, M. D.; Green, A. R.; Heathcliffe, G. R.; Meacock, P. A.;Schuch, W.; Scanlon, D. B.; Atkinson, T. C.; Newton, C. R.; Markham,A. F.: Total synthesis of a human leukocyte interferon gene. Nature 292:756–762, 1981.

[0995] 593.Fountain, J. W.; Karayiorgou, M.; Taruscio, D.; Graw, S. L.; Buckler,A. J.; Ward, D. C.; Dracopoli, N. C.; Housman, D. E.: Genetic andphysical map of the interferon region on chromosome 9p. Genomics 14:105–112, 1992.

[0996] 594.Gillespie, D.; Carter, W.: Concerted evolution of human interferonalpha genes. J. Interferon Res. 3: 83–88,

1983.

[0997]   595.Hayden, F. G.; Albrecht, J. K.; Kaiser, D. L.; Gwaltney,
J. M.,Jr.: Prevention of natural colds by contact prophylaxis
with intranasalalpha-2-interferon. New Eng. J. Med. 314:
71-75, 1986.

[0998]   596.Hitzeman, R. A.; Hagie, F. E.; Levine, H. L.; Goeddel,
D. V.;Ammerer, G.; Hall, B. D.: Expression of a human
gene for interferonin yeast. Nature 293: 717-722, 1981.

[0999]   597.Imai, M.; Sano, T.; Yanase, Y.; Miyamoto, K.; Yone-
hara, S.; Mori,H.; Honda, T.; Fukuda, S.; Nakamura, T.;
Miyakawa, Y.; Mayumi, M.: Demonstration of two subtypes
of human leukocyte interferon (IFN-alpha)by monoclonal
antibodies. J. Immun. 128: 2824-2825, 1982.

[1000]   598.Isaacs, D.; Clarke, J. R.; Tyrrell, D. A. J.; Webster, A. D.
B.;Valman, H. B.: Deficient production of leucocyte inter-
feron (interferon-alpha)in vitro and in vivo in children with
recurrent respiratory tractinfections. Lancet II: 950-952,
1981.

[1001]   599.Lawn, R. M.; Adelman, J.; Dull, T. J.; Gross, M.; Goed-
del, D.;Ullrich, A.: DNA sequence of two closely linked hu-
man leukocyte interferongenes. Science 212: 1159-1162,
1981.

[1002]   600.Lawn, R. M.; Goeddel, D. V.; Ullrich, A.: The human

interferongene family.(Abstract) Sixth Int. Cong. Hum. Genet., Jerusalem 55only, 1981.

[1003] 601.Miyata, T.; Hayashida, H.: Recent divergence from a common ancestorof human IFN-alpha genes. Nature 295: 165-168, 1982.

[1004] 602.Mory, Y.; Chernajovsky, Y.; Feinstein, S. I.; Chen, L.; Weissenbach,J.; Revel, M.: Expression of the cloned human interferon beta-1 genein E. coli.(Abstract) Sixth Int. Cong. Hum. Genet., Jerusalem 56only, 1981.

[1005] 603.Huang, Y. Z.; Won, S.; Ali, D. W.; Wang, Q.; Tanowitz, M.; Du,Q. S.; Pelkey, K. A.; Yang, D. J.; Xiong, W. C.; Salter, M. W.; Mei,L.: Regulation of neuregulin signaling by PSD-95 interacting withErbB4 at CNS synapses. Neuron 26: 443-455, 2000.

[1006] 604.Kremmidiotis, G.; Baker, E.; Crawford, J.; Eyre, H. J.; Nahmias,J.; Callen, D. F.: Localization of human cadherin genes to chromosomeregions exhibiting cancer-related loss of heterozygosity. Genomics 49:467-471, 1998.

[1007] 605.Pestka, S.: The human interferons--from protein purificationand sequence to cloning and expression in bacteria: before, between,and beyond. Arch. Biochem. Biophys. 221: 1-37, 1983.

[1008] 606.Sehgal, P. B.; Sagar, A. D.; Braude, I. A.: Further het-

erogeneityof human alpha-interferon mRNA species. Science 214: 803-805, 1981.

[1009]   607.Shows, T. B.; Sakaguchi, A. Y.; Naylor, S. L.; Goeddel, D. V.;Lawn, R. M.: Clustering of leukocyte and fibroblast interferon geneson human chromosome 9. Science 218: 373-374, 1982.

[1010]   608.Slate, D. L.; D'Eustachio, P.; Pravtcheva, D.; Cunningham, A.C.; Nagata, S.; Weissmann, C.; Ruddle, F. H.: Chromosomal locationof a human alpha interferon gene family. J. Exp. Med. 155: 1019-1024,1982.

[1011]   609.Trent, J. M.; Olson, S.; Lawn, R. M.: Chromosomal localizationof human leukocyte, fibroblast and immune interferon genes by meansof in situ hybridization. Proc. Nat. Acad. Sci. 79: 7809-7813, 1982.

[1012]   610.Ullrich, A.; Gray, A.; Goeddel, D. V.; Dull, T. J.: Nucleotidesequence of a portion of human chromosome 9 containing a leukocyteinterferon gene cluster. J. Molec. Biol. 156: 467-486, 1982.

[1013]   611.Virelizier, J. L.; Griscelli, C.: Defaut selectif de secretiond'interferon associe a un deficit d'activite cytotoxique naturelle. Arch.Franc. Pediat. 38: 77-81, 1981.

[1014]   612.Virelizier, J. L.; Lenoir, G.; Griscelli, C.: Persistent Epstein-Barrvirus infection in a child with hypergammaglob-

ulinaemia and immunoblasticproliferation associated with a selective defect in interferon secretion. Lancet II:231-234, 1978.

[1015] 613.Jung, J.; Zheng, M.; Goldfarb, M.; Zaret, K. S.: Initiation ofmammalian liver development from endoderm by fibroblast growth factors. Science 284:1998-2003, 1999.

[1016] 614.Wijnen, J. T.; Oldenburg, M.; Bloemendal, H.; Meera Khan, P.:GS(gamma-S)-crystallin (CRYGS) assignment to chromosome 3. (Abstract) Cytogenet.Cell Genet. 51: 1108 only, 1989.

[1017] 615.den Dunnen, J. T.; Jongbloed, R. J. E.; Geurts van Kessel, A. H.M.; Schoenmakers, J. G. G.: Human lens gamma-crystallin sequencesare located in the p12-qter region of chromosome 2. Hum. Genet. 70:217-221, 1985.

[1018] 616.Bierhuizen, M. F. A.; Mattei, M.-G.; Fukuda, M.: Expression ofthe developmental I antigen by a cloned human cDNA encoding a memberof a beta-1,6-N-acetylglucosaminyltransferase gene family. Genes-Dev. 7: 468-478, 1993.

[1019] 617.Lin-Chu, M.; Broadberry, R. E.; Okubo, Y.; Tanaka, M.: The i phenotypeand congenital cataracts among Chinese in Taiwan (Letter) Transfusion 31:676-677, 1991.

[1020] 618.Ogata, H.; Okubo, Y.; Akabane, T.: Phenotype i asso-

ciated withcongenital cataract in Japanese. Transfusion 19: 166-168, 1979.

[1021] 619.Yeh, J.-C.; Ong, E.; Fukuda, M.: Molecular cloning and expressionof a novel beta-1,6-N-acetylglucosaminyltransferase that forms core2, core 4, and I branches. J. Biol. Chem. 274: 3215-3221, 1999.

[1022] 620.Yu, L.-C.; Twu, Y.-C.; Chang, C.-Y.; Lin, M.: Molecular basisof the adult i phenotype and the gene responsible for the expressionof the human blood group I antigen. Blood 98: 3840-3845, 2001.

[1023] 621.Seri, M.; Celli, I.; Betsos, N.; Claudiani, F.; Camera, G.; Romeo,G.: A cys634gly substitution of the RET proto-oncogene in a familywith recurrence of multiple endocrine neoplasia type 2A and cutaneouslichen amyloidosis. Clin. Genet. 51: 86-90, 1997.

[1024] 622.Hofstra, R. M. W.; Sijmons, R. H.; Stelwagen, T.; Stulp, R. P.;Kousseff, B. G.; Lips, C. J. M.; Steijlen, P. M.; Van Voorst Vader,P. C.; Buys, C. H. C. M.: RET mutation screening in familial cutaneouslichen amyloidosis and in skin amyloidosis associated with multipleendocrine neo-plasia. J. Invest. Derm. 107: 215-218, 1996.

[1025] 623.van Leeuwen, F. W.; de Kleijn, D. P. V.; van den Hurk,

H. H.; Neubauer,A.; Sonnemans, M. A. F.; Sluijs, J. A.; Koycu, S.; Ramdjielal, R.D. J.; Salehi, A.; Martens, G. J. M.; Grosveld, F. G.; Burbach, J.P. H.; Hol, E. M.: Frameshift mutants of beta-amyloid precursor proteinand ubiquitin-B in Alzheimer's and Down patients. Science 279: 242-247,1998.

[1026] 624.Webb, G. C.; Baker, R. T.; Fagan, K.; Board, P. G.: Localizationof the human UbB polyubiquitin gene to chromosome band 17p11.1-17p12. Am.J. Hum. Genet. 46: 308-315, 1990.

[1027] 625.Greco, A.; Ittmann, M.; Barletta, C.; Basilico, C.; Croce, C. M.;Cannizzaro, L. A.; Huebner, K.: Chromosomal localization of humangenes required for G(1) progression in mammalian cells. Genomics 4:240-245, 1989.

[1028] 626.Ittmann, M.; Greco, A.; Basilico, C.: Isolation of the human genethat complements a temperature-sensitive cell cycle mutation in BHKcells. Molec. Cell. Biol. 7: 3386-3393, 1987.

[1029] 627.Zhong, G.; Fan, P.; Ji, H.; Dong, F.; Huang, Y.: Identificationof a chlamydial protease-like activity factor responsible for thedegradation of host transcription factors. J. Exp. Med. 193: 935-942,2001.

[1030] 628.Koyama, K.; Sudo, K.; Nakamura, Y.: Mapping of the

human nicotinicacetylcholine receptor beta-3 gene (CHRNB3) within chromosome 8p11.2. Genomics 21:460-461, 1994.

[1031] 629.Willoughby, J. J.; Ninkina, N. N.; Beech, M. M.; Latchman, D. S.;Wood, J. N.: Molecular cloning of a human neuronal nicotinic acetylcholinereceptor beta-3-like subunit. Neurosci. Lett. 155: 136-139, 1993.